Chemotherapy for Cancer and the Aging Brain: Blessing or Burden?

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ABSTRACT

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Purpose: The proportion of the United States population in older adulthood is growing rapidly, and with that growth comes an increase in diseases such as cancer. As rates of illness increase, there is a concomitant increase in cognitive and psychological correlates of illnesses like cancer. There is evidence that some cancer treatments, particularly chemotherapy, affect cognition for cancer patients, although these results are inconsistent. Additionally, depression, and other health factors such as activities of daily living (ADLs) have been found to relate to cognitive impairment among older adults with cancer. *Method:* The current study used latent class growth analysis (LCGA) to explore longitudinal data from the Health and Retirement Study. The primary goal was to investigate possible trajectories of cognitive functioning in older adults diagnosed with, and surviving cancer. Possible psychological, health, and demographic predictors of membership in these cognitive trajectories were investigated. *Results:* Findings indicated that three classes of cognitive functioning best fit the data: these were High Recall, Middle Recall and Low Recall Classes, which represented fairly stable trajectories from pre-diagnosis to a period four years later. Various covariates of class membership were included in the analyses. Treatment with chemotherapy significantly predicted membership in the High Recall Class, however this finding is accounted for by an interaction with younger age. More symptoms of depression after diagnosis (but not prior to diagnosis) were significantly predictive of membership in the Low Recall Class. A higher self-reported probability of living to the age of 85 pre-diagnosis predicted membership in the High Recall Class, and greater difficulty with ADLs post-diagnosis predicted membership in the Low Recall Class. Finally, individuals in the High Recall Class were significantly more likely to be younger, female, and more highly educated, when compared to both the Middle and Low Recall Classes. *Limitations:* The current study is limited by the wide spacing of data collection and dearth of sensitive and varied measures of cognitive functioning, which in turn limits the generalizability and specificity of the findings. Additionally, a lack of data on cancer type, staging and treatment variables make more nuanced analysis difficult. It is not possible to generalize these findings to individuals who passed away within two years of their diagnosis, not to individuals of minority status, who were underrepresented in this sample. *Conclusions:* These results may inform the understanding of cognitive functioning in older adults surviving cancer, as it relates to psychological, demographic and other health factors, with implications for timing and targeting of interventions.

TABLE OF CONTENTS

List of Tables and Figures

Tables

Figures

Acknowledgments

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Dedication

I dedicate my dissertation to my grandmother (and also dearest friend), Arlene Horowitz, whose love and own academic work inspired me to work hard and carefully. Additionally, her unwavering love and care for her own mother and my namesake, Ruth Karas, during her illness and treatment, were the groundwork for this topic.

Chemotherapy for Cancer and the Aging Brain: Blessing or Burden?

In the current era, the United States population is living longer, with the number of individuals over the age of 65 expected to double in the next 25 years (Kinsella & Wan, 2009). However, as the population ages, there is a marked increase in the prevalence of many age-related diseases (Hebert, Scherr, Bienias, Bennett, & Evans, 2003; Yancik, 1997), including cancer. In fact, research has shown that the single most common risk factor for cancer is aging, with over 60% of cancers diagnosed in individuals over the age of 65 (Howlader et al., 2011; Smith, Smith, Hurria, Hortobagyi, & Buchholz, 2009).

Though epidemiologic studies have shown a stabilization of cancer incidence rates, as well as a decrease in deaths overall, older adults in general and older women and minorities in particular are still at the greatest risk of mortality (Edwards et al., 2002). As risk factors for cancer death have been investigated, so too have associations with survivorship, particularly as the number of cancer survivors increases, and continues to age. Indeed, it is estimated that by the year 2020, 63% of cancer survivors will be over the age of 65 (Hewitt, Rowland, & Yancik, 2003). Just as cancer is associated with general health, psychological, and cognitive problems among older adults, so too does survivorship impact health comorbidities, psychological distress, and difficulties with instrumental activities of daily living (Gotay & Muraoka, 1998).

The increase in cancer incidence, as well as the greater chance of survival due to early detection and advances in treatment, means that more individuals may encounter the neurotoxic side effects of certain treatments – particularly physical effects such as the nausea, vomiting and hair loss associated with chemotherapy (Argyriou, Assimakopoulos, Iconomou, Giannakopoulou, & Kalofonos, 2011). Cognitive changes during a course of treatment with

chemotherapy have been reported as well, including difficulty with memory, attention, and concentration (Ahles et al., 2002; Vardy & Tannock, 2007). Though reports of "chemo fog" or "chemo brain" have appeared in the literature since the 1970's (Silberfarb, 1983), inconsistencies in research findings and methodological problems have impeded generalization. Of particular relevance is the dearth of studies investigating post-chemotherapy cognitive impairments in older adults.

There have been inconsistent findings in studies of chemotherapy for cancer and cognition in late life. These inconsistencies have been attributed to depressive symptoms associated with chemotherapy, other health comorbidities, and degree of cognitive impairment prior to treatment (Ahles & Saykin, 2007). Additionally, there are many studies that have failed to observe any cognitive changes after treatment with chemotherapy across a range of cancer types and patient demographics; including gender, age and education level (e.g. Donovan et al., 2005; Jenkins et al., 2006; Keating, Nørredam, Landrum, Huskamp, & Meara, 2005; Porter, 2013; Shaffer et al., 2012), with other studies reporting a range of cognitive difficulties from the start of treatment to long after the onset of remission (Ahles et al., 2002; Argyriou et al., 2011; Vardy & Tannock, 2007). Along with the inconsistency in results, heterogeneity in regard to demographic and other health factors further complicate the present understanding of the relationship between cognition and cancer in late life.

Regardless of the many challenges, there has been an increased focus on chemotherapy-induced cognitive impairment (CICI) in the literature, with particular interest in finding which individuals are most likely to be at risk, what treatment circumstances evoke the greatest amount of risk, and how survivors of cancer may be affected over time (e.g.; Ahles et al., 2002; Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Tchen, et al., 2003; Vardy &

Tannock, 2007; Vearncombe & Pachana, 2009). Although the number of studies on CICI has increased, Wefel and Schagen (2012) found that of 53 studies published between 1995 and 2012, individuals over the age of 50 were studied in only six (11% of studies). Although half of the women diagnosed with breast cancer are over the age of 65, only two studies have been published about this age group. This discrepancy between research populations and patient populations is complicated by the ageism already documented in hospital settings treating older adult patients (Bond et al., 2003; Janssen-Heijnen et al., 2007; Peake, Thompson, Lowe & Pearson, 2003). Furthermore, the paucity of research about older adults raises the possibility that older patients may not only be at greater risk for cognitive side effects of cancer treatment (Heflin et al., 2005; Heflin, Pollak, Kuchibhatla, Branch, & Oddone, 2006), but that their treating physicians may also assume that any cognitive deficits are attributable to age, rather than to the side effects of treatment (Schroyen, Adam, Jerusalem, & Missotten, 2015).

Finally, as the population ages, the cognitive and emotional functioning of older adults has wide-ranging implications for the quality of life and meaning in later life, as well as for families, communities and society at large. In light of emerging research indicating the importance of contributions to society by older adults, many of whom are prosocial (Midlarsky & Hannah, 1989; Midlarsky & Kahana, 2007; Kahana, Bhatta, Lovegreen, Kahana, & Midlarsky, 2013; Midlarsky, Kahana, & Belser, 2015), it is especially vital to study the effect of cancer treatment and other health outcomes associated with cancer on cognitive competence, and on functioning in daily life. Additionally, with the increased rates of survival from cancer, it is vital to investigate the cognitive, physical, and emotional functioning both among older adults with active cancer and those in remission. Thus, this study was designed as a longitudinal investigation of the relationships among cancer, chemotherapy, health and cognition in late life.

Cognitive impairment associated with chemotherapy

Chemotherapy-induced cognitive impairment (CICI) has been found to include impairment of memory, learning, concentration, attention, executive function, processing speed and visuospatial skills in numerous articles (e.g. Anderson-Hanley et al., 2003; Argyriou et al., 2011; Kreukels, Schagen, Ridderinkhof, Boogerd, Hamburger & van Dam, 2005; Wefel & Schagen, 2012). Estimates of the duration of these symptoms range from the period concurrent with treatment to a persistence during the period when the patient is in remission (Argyriou et al., 2011; Kreukels et al., 2006; Vardy & Tannock, 2007). Indeed, several clinical studies estimated that the prevalence of long-term cognitive impairment after chemotherapy (CICI) affects between 16% and 75% of patients. This is even after controlling for the severity of cancer, psychological symptoms and demographic factors (Anderson-Hanley et al., 2003; Kreukels et al., 2006; Tchen, et al., 2003; Vardy & Tannock, 2007).

The neuropsychological dysfunction reported in association with chemotherapy has been somewhat inconsistent across studies (Vardy & Tannock, 2007), although it is usually described as primarily related to attention, verbal and visual memory, and processing speed. These deficits are often understood in the context of the Reitan/Wolfson assessment model of neuropsychological functioning (Reitan & Wolfson, 2003), which describes the way information is processed from external stimuli, and ultimately encoded for later retrieval. The model posits that a certain degree of alertness and ability to sustain attention and concentration is required in order for sensory areas to process information, which is then encoded in deeper, subcortical structures. It is possible, then, that if initial attention is compromised due to neurotoxic side effects of treatment, that encoding and subsequent retrieval attempts will be compromised as

well (Anderson et al., 2000). Indeed, similar cognitive difficulties have been described in illnesses such as Parkinson's disease and HIV, with or without adjuvant treatment that might compromise neuropsychological abilities (Butters et al., 1990; Massman, Delis, Butters, Levin, & Salmon, 1990; Whittington, Pod, & Kan, 2000).

Many variables have been investigated as possible risk factors for the development of these cognitive impairments, including structural brain changes, type of cancer, type and dosage of chemotherapy agent, degree of cognitive impairment prior to the cancer diagnosis, and other health, psychological and demographic correlates (e.g. Ahles & Saykin, 2007; Vardy et al., 2006; Wefel & Schagen, 2012). The multitude of associated factors, and the limited knowledge of their complex interplay, certainly complicates the ability to isolate specific predictors and effects of chemotherapy on cognition.

Of particular relevance, cognitive impairment prior to treatment (and even prior to cancer diagnosis) would place an individual at greater risk for developing CICI (Ahles & Saykin, 2007; Cimprich et al., 2010). There may be genetic factors that predispose an individual to developing both cancer and cognitive impairment in late life, though it is nearly impossible to disentangle the multitude of possible factors involved, particularly among older adults (Rolig & McKinnon, 2000). Additionally, lifestyle choices throughout adulthood are likely to affect both cognitive impairment and risk factors for cancer. For example, smoking has been shown to place individuals at risk for dementia, and is a known cause of lung cancer – a link that is especially salient for the current cohort of older adults (Anstey, von Sanden, Salim, & O'Kearney, 2007).

The cancer patients most frequently studied in regard to cognitive impairment after chemotherapy are breast cancer survivors (e.g. Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Castellon et al., 2004; Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Zunini et al.,

2013). It is difficult to determine whether breast cancer survivors are more studied because they have the greatest incidence of CICI, or for other reasons. For example, they may be more frequently studied because the fact the higher survival rate makes any treatment side effects, including cognitive impairment after chemotherapy, both more salient and more likely. Another possibility is that they are frequently studied because of the social and political organizing around survivors' issues evokes interest and attention (Corbett & Mori, 1999; King, 2004).

It is also the case that the effect of chemotherapy on cognitive functioning has received more attention for individuals with non-central nervous system (CNS) cancers such as breast cancer, than CNS cancers. This is likely due to the fact that cognitive impairment associated with CNS cancer is more likely to be a result of the cancer itself rather than the treatment, since CNS cancer often affects the brain (Ahles & Saykin, 2007). Indeed, there have been reports of chemotherapy *improving* cognition in CNS cancers, in cases in which chemotherapy has the result of reducing the size and effect of these cancers (Hilverda et al., 2010; Wefel et al., 2011; Wefel & Schagen, 2012). Although some cancers have received more attention than others in their association with CICI, several studies have failed to find a significant relationship between cancer type and stage on outcomes associated with chemotherapy (e.g. Burton, Galatzer-Levy, & Bonanno, 2014; Hipkins, Whitworth, Tarrier, & Jayson, 2004).

In regard to brain changes associated with adjuvant treatment, magnetic resonance imaging (MRI) studies of cancer patients who have undergone chemotherapy have found a reduction of volume in the frontal cortex, along with demyelination of white matter tracts, both of which have been associated with deficits in working memory and executive functions (Saykin, Ahles, & McDonald, 2003; Stemmer, Stears, Burton, Jones, & Simon, 1994). When functional magnetic resonance imaging (fMRI) has been used to assess brain activity during a working

memory task, a decrease in overall brain activation has been reported among breast cancer survivors who underwent adjuvant chemotherapeutic treatment, compared to healthy controls (Zunini et al., 2013). It is worth noting, however, that some of the patterns of lessened activation of the bilateral insula, orbitofrontal cortex, and left insula were explained not only by recent treatment with chemotherapy, but also by pre-treatment differences, including depression, anxiety and fatigue (Cimprich et al., 2010; Zunini et al., 2013). These findings suggest that there may be an interaction between neurotoxic factors and diverse physical and psychological processes for many patients.

Though several studies have found links between chemotherapy and cognitive impairment (for reviews, see Ferguson & Ahles, 2003; Vardy & Tannock, 2007), many of the findings have been inconsistent, and methodological limitations have raised concerns about the generalizability of the findings. These limitations include sampling individuals after they have been diagnosed, small sample sizes, and lack of prospective data on various health and cognitive indices among participants. As previously noted, a wide range of prevalence estimates have been reported, with different rates reported across studies, and some failing to find any effect of chemotherapy at all (e.g. Donovan et al., 2005; Jenkins et al., 2006; Keating, Nørredam, Landrum, Huskamp, & Meara, 2005; Porter, 2013; Shaffer et al., 2012). Additionally, studies subsequent to those initially showing cognitive deficits have reported no discernible differences several years following treatment (Schagen et al., 2002). These studies raise questions about the ability to reliably discern CICI among cancer patients after treatment and into remission, as well as whether the cognitive impairments observed are actually a result of treatment with chemotherapy. Further, the interplay of demographic factors with comorbid health and psychological variables becomes even more complicated among older adults.

Depression and cognition in cancer

In many studies of CICI, factors such as fatigue, and psychological distress, particularly depression and anxiety, have been cited as possible confounds of the relationship between chemotherapy and cognitive impairment (Phillips & Bernhard, 2003; Tchen et al., 2003). Indeed, these variables have been found to relate to cognitive functioning even in the absence of a cancer diagnosis (Massman, Delis, Butters, Dupont, & Gillin, 1992). These deficits have anatomical correlates, such as subcortical dysfunction, and neuropsychological correlates that are very similar to those associated with chemotherapy and cancer, Parkinson's disease, and HIV, among others (Butters et al., 1990; Massman, Delis, Butters, Levin, & Salmon, 1990).

Symptoms of psychopathology have long been associated with diagnosis and treatment of cancer of various types, and have been shown to persist long after remission among certain individuals (e.g. Burgess et al., 2005; Chochinov, 2001; Derogatis et al., 1983). Furthermore, depression and anxiety symptoms are often associated with cognitive deficits that may mimic neurotoxic symptoms associated with chemotherapy (McClintock, Husain, Greer, & Cullum, 2010; Silberfarb, Philibert, & Levine, 1980). Depression alone has been implicated as a risk factor for cancer and other stress-related health problems, with higher rates post-diagnosis than for other major medical conditions (Polsky et al., 2005). The added burden of depression may also incur greater allostatic load (accumulation of negative health factors; McEwen, 1998). The comorbidity of cancer and depression is associated with poorer outcomes than either cancer or depression alone (Moussavi et al., 2007). Additionally, treatment with chemotherapy has been shown to be associated at onset and/or increase depression among adults and older adults with cancer, even years after diagnosis (Burton, Galatzer-Levy, & Bonanno, 2014).

What makes the separation of the depression from the biological impact of chemotherapy so difficult is that even if cognitive impairment is neurobiological or genetic in origin, individuals may have symptoms of depression resulting from their decrement in functioning and lower quality of life after treatment (Castellon et al., 2004; Harrington, Hansen, Moskowitz, Todd, Feuerstein, 2010; Jenkins et al., 2006). These issues demonstrate how important it is to investigate these topics prospectively, in an attempt to establish whether psychological or biological variables (or a combination), are risk factors or consequences of cognitive deficits in cancer patients (Jenkins et al, 2006). Furthermore, it is possible that contributing factors have differential effects at different ages. Indeed, much of the research that has been done fails to take into consideration the specific challenges faced by older adults with cancer.

Cognition in late life

While cognition in older adults may be further compromised by medical issues such as cancer, there is a certain amount of decline in domains such as attention and rote verbal memory that is associated with normal aging (Craik, 1994). Indeed, studies of healthy, cognitively intact older adults have shown profiles of working memory that resemble young adults with divided attention and executive dysfunction, indicating that some decline in the ability to attend to, process, and ultimately encode information is expected with age (Anderson et al., 2000).

Demographic characteristics have been associated with cognition in late life as well, with the level of education and intelligence often cited as protective factors, leading to the concept of cognitive reserve. Cognitive reserve leads to slowing down of functional decline even in the presence of neurodegeneration (Stern, 2003). On the other hand, other studies have shown lower levels of education to be protective against cognitive decline in late life, possibly because of a floor effect for such individuals on neuropsychological testing (Ardila, Ostrovsky-Solis, Rosselli,

& Gomez, 2000). Factors, such as gender, race, and age are related to cognitive impairment, with the oldest women generally exhibiting the steepest decline (Proust-Lima et al., 2008), though this may be accounted for by gender discrepancies in life expectancy and historical barriers to higher education for women and minorities. Additionally, lower socioeconomic status across the lifespan is associated with cognitive decline (Rabbitt, Donlan, Watson, McInnes, & Bent, 1995).

In addition to normal change in cognition associated with aging, and demographic correlates of cognitive impairment, the presence of comorbid health concerns (physical and psychological) have been shown to affect neuropsychological outcomes (Comijs, Deeg, Dik, Twisk, & Jonker, 2002; Seeman, McEwen, Rowe, & Singer, 2001). Some studies have even shown relationships among self-perceptions of health status and cognition (Shrira et al., 2011), and on depression, that is also related to cognition in late life (Cole & Dendukuri, 2003). This may be especially problematic for those who believe that physical, emotional and cognitive decline are inevitable parts of the aging process, as these individuals may be less likely to seek preventive health care services (Sarkisian, Hays, & Mangioni, 2002).

Finally, cognition has been associated with functional indices, particularly the ability to perform activities of daily living (ADLs) such as walking one block, standing up from a sitting position without assistance, and taking care of one's own personal hygiene (Freedman et al., 2013). Indeed, cognitive changes among older adults have been associated with lower fluency with ADLs in a number of studies (McGuire, Ford, & Ajani, 2006). In addition, difficulty with physical tasks, exercise, and a more stationary lifestyle have been associated with impaired cognition (Tabbarah, Crimmins, & Seeman, 2002), though at times this association has been bolstered by other factors like depression (Atkinson et al., 2007). As most older adults, even those considered healthy, experience some comorbid medical conditions and declines in

functioning (Freedman et al., 2013), adding the additional burden of an illness as serious as cancer can increase the likelihood of impairment.

Factors associated with cancer in late life

Cancer and cancer treatment in late life are increasingly important as the United States population ages (Krtolica & Campisi, 2002). Additionally, it is estimated that by the year 2030, 70% of new cancer diagnoses will be made in individuals over the age of 65 (Smith et al., 2009). With these facts in mind, it is vital that an emphasis be placed not only on the effective treatment of cancer in the elderly, but also on the quality of life and psychosocial issues associated with illness and treatment in this population. Integrative research is particularly important because of the heterogeneity of older adults in every domain, from cultural concerns, to physical and cognitive functioning, to educational level, to economic status (Puts, Papoutsis, Springall, & Tourangeau, 2012).

Among older adults, as in younger people, cancer diagnosis, treatment and survivorship have been associated with psychological distress (e.g. Burgess et al., 2005; Chochinov, 2001). Indeed, one study found that over 25% of late life long-term cancer survivors evidenced clinical levels of depression (Deimling, Kahana, Bowman, & Schaefer, 2002). Because depression and other psychological issues are also associated with cognitive deficits, medical illness, and quality of life concerns (Butters et al., 2000; Blazer, 2003), understanding the interplay of depression with cancer and other functional concerns in this population is extremely important.

Additionally, it is increasingly clear that responses to cancer diagnosis and treatment are influenced by the aging process (Hurria, Naylor, & Cohen, 2013). For example, because age-related physiological changes occur in the renal and hepatic systems of older adults, there are barriers to efficacious pharmacotherapy interventions in the sense that chemotherapies may be

harmful to the aging liver and kidney (Puts et al., 2012). It is also vital to address the fact that older adults with new diagnoses of cancer are likely to have other comorbid health concerns that could affect their prognosis, treatment options, and chance of survival (Yancik, Ganz, Varricchio, Conley, 2001). Additional barriers, such as poverty, stigma related to cancer, and lack of access to pertinent information regarding diagnosis and treatment will contribute to the difficulty of getting good medical care among older adults, particularly among minority group members (Hurria et al., 2008). Because of these and other related issues, it is possible that cancer deaths will increase in the coming decades (Smith et al., 2009).

Finally, ageism in the medical treatment of older adults, especially in hospital settings, has been widely documented. Some studies have found negative attitudes toward elderly patients most prevalent in doctors uninterested in working with older people, often because it's "not worth it" since the older individual has "lived long enough" that they may fail to thrive even if cured, or hasn't many years to live anyway (Leung, LoGiudice, Schwarz, & Brand, 2011). Certain physicians rate older people as having low eligibility for cancer screening, treatment and participation in clinical research trials based on both on chronological age and on medical comorbidities (Heflin, Pollak, Kuchibhatla, Branch, & Oddone, 2006; Schroyen, Adam, Jerusalem, & Missotten, 2015). This ageism is particularly distressing in light of research showing that older adults primed with negative stereotypes about aging evidenced a weaker will to live than those not exposed to ageist stereotypes (Levy, Ashman, & Dror, 2000). Additionally, an individual's subjectively perceived health status has been found to independently predict mortality (Idler & Benyamini, 1997), highlighting the importance of positive interactions with medical professionals around identity issues related to age and illness. Fortunately, there has

recently been an increase in effort to train oncologists and other clinicians to be competent at working with older adults (Hurria et al., 2008).

Limitations of existing research

There are many limitations to the existing research on cognitive changes in cancer, including those associated with chemotherapy. These limitations make it difficult to generalize findings, gain consensus among scientists about implications for various patient populations, predict outcomes over time and, importantly, to develop effective cognitive interventions for suffering patients. The most serious limitations are sampling biases, the fact that most research is cross-sectional rather than longitudinal, and the dearth of research addressing these phenomena in older adults.

Even though CICI has been reported and studied for several decades, there is a surprising lack of measurement instruments for assessing cancer-related cognitive functioning (Vardy et al., 2006). There are other difficulties as well, such as sampling and methodological biases associated with studies of patient populations - for example, arbitrary cutoff points for measures, small sample sizes, pre-existing differences among patients sampled, and the relative paucity of follow-up data collection (Altman & Lyman, 1998). Furthermore, the measures used may not be sensitive enough to measure changes over time, particularly if those changes are small. An additional problem is that many of the measures used have practice effects, and patients may be re-tested too soon for these effects to wear off (McCaffrey, Duff, & Westervelt, 2000; Salinsky, Storzbach, Dodrill, & Binder, 2001). The use of neuropsychological tests designed to measure baseline cognitive functioning may not capture subtle changes in executive functioning and working memory, especially for older adult patients (Au et al., 2004; Salthouse, 2009).

Perhaps the most serious limitation to the existing research on CICI is that most studies have been cross-sectional rather than longitudinal (Argyriou et al., 2011). The lack of testing at a time prior to diagnosis and treatment onset as well as long-term follow up in these samples renders it difficult to establish a temporal relationship between cognitive capacity and treatment (Campbell, Stanley, & Gage, 1963). Some prospective studies have been undertaken in the past few years. However, even these studies do not clearly separate cancer diagnosis from the other factors that may affect cognitive functioning (e.g. Falleti et al., 2005; Minsini et al., 2008; Zunini et al., 2013). Further study is needed in large, nationally representative samples followed over a period of years, with data collected in a context unrelated to cancer diagnosis or treatment to limit expectancy effects and other response biases (Juster & Suzman, 1995; Rosenthal, 1965).

In addition to the problematic nature of some research designs employed to test hypotheses about CICI, there is also the sampling difficulty inherent in the heterogeneity of types of cancer and the diverse treatments administered. This is true particularly when small sample sizes are used (Vardy, et al., 2006), people are sampled only after their diagnoses (Vardy et al., 2006), and when other factors such as mood are not controlled (Phillips & Bernhard, 2003). Certainly, there is considerable heterogeneity in the demographic and health characteristics of cancer patients and survivors, particularly in late life (Jung & Wickrama, 2008).

Several recent studies on cognitive functioning in late life have found no evidence that chemotherapy affects cognitive functioning (Keating et al., 2005; Porter, 2013). However, these studies did not assess more nuanced changes in cognition over time, and failed to identify significant covariates. One study that employed a longitudinal design demonstrated that chemotherapy had a significant impact on persistent depression among cancer survivors, when these survivors were compared with those who received other forms of treatment (Burton,

Galatzer-Levy, & Bonanno, 2014). This indicates the importance of continuing to investigate the impact of chemotherapy and other health and mood factors on cognition in late life. Such studies should employ sensitive research designs, such as prospective longitudinal designs, and statistical techniques such as latent growth modeling (Jung & Wickrama, 2008).

The current study

Current research focusing on post-cancer cognitive impairment suggests that demographic factors, treatment with chemotherapy, poor health and functioning, and depressive symptoms are all significantly related to cognitive functioning after treatment. However, many of these studies are cross-sectional in design, and among those with a prospective design, few have measured cognitive functioning prior to diagnosis. Additionally, many studies lack a comparison group, particularly those diagnosed with cancer that received other types of treatment (particularly radiotherapy or surgical intervention), and did not receive chemotherapy. This study offers a unique opportunity to analyze prospective data within an understudied population over time, with implications for intervention and treatment.

The current study will employ longitudinal data in order to analyze cognitive functioning from the period two years prior to cancer diagnosis, to the time point immediately following diagnosis and initial treatment (at which point the greatest treatment effects may be observed), and then to the period four years after the start of treatment. Additionally, hypothesized demographic, health and psychological predictors of cognitive functioning will be investigated among older adults diagnosed with cancer.

It has been increasingly clear in the last several decades of research that older adults continue to contribute to society long after retirement. Emerging research on prosocial behavior in late life indicates that individuals are eager to help others, even if they are not in perfect health

themselves (Midlarsky & Hannah, 1989; Midlarsky & Kahana, 2007; Kahana et al., 2013; Midlarsky, Kahana, & Belser, 2015). Because of the rapid aging of the United States population and the associated implications for society (in terms of cost of care), it is valuable to seek greater understanding of factors that might impede older individuals from aging successfully, and from experiencing life as meaningful after cancer treatment.

Hypotheses and research questions

In previous research, factors such as demographic factors, treatment with chemotherapy, functional and health concerns, and depressive symptoms have been found to be associated with impairment in cognitive functioning after treatment. In this study of older adults, it is hypothesized that the relationships among these variables will be similar to those found in the literature. It is predicted that exposure to treatment with chemotherapy (Vardy & Tannock, 2007), and depressive symptoms (Burton, Galatzer-Levy, & Bonanno, 2014), will predict cognitive decline over time, in addition to other demographic and functional factors. The hypotheses, followed by the research question, are as follows.

1. In older adult cancer patients, treatment with chemotherapy will be associated with lower cognitive functioning over time, compared with treatment with radiation or surgery.
2. More depressive symptoms following diagnosis and onset of treatment will predict lower cognitive functioning over time.
3. Difficulty with ADLs following diagnosis and onset of treatment will predict lower cognitive functioning over time.
4. Higher level of education and younger age will predict better cognitive functioning over time.

5. Will a higher subjective health rating prior to diagnosis predict better cognitive functioning over time, even after diagnosis and treatment?

Method

Participants

The sample consists of participants in the Health and Retirement Study (HRS), an ongoing study sponsored by the National Institute on Aging (grant number NIA U01AG009740), collected by scientists at the University of Michigan. This study was undertaken to better understand various aspects of aging among Americans, including health factors. It began in 1992, with sample of individuals born between 1931 and 1941. Every six years, a new cohort of older adults has been added to the sample (such as the War Baby, Children of Depression Era, and Early Baby Boomer cohorts), while previous samples continued to be interviewed along with their spouses. Three of the five groups sampled thus far came from an initial sampling effort in 1992, when 69,337 households were screened for eligible participants. Of this number, 59,918 households were identified as eligible (Juster & Suzman, 1995), and a multi-stage, clustered area probability frame approach was used to select 15,497 participants (Sonnega et al., 2014). Subsequent cohorts were sampled from the Medicare enrollment database. Ultimately, face-to-face interviews of selected participants and their spouses (oversampling for certain minority groups; Juster & Suzman, 1995) have been conducted every two years since 1992. Results of the most recent wave of data were released in the year 2012. For each wave, response rates were between 88% and 89.4%. These data have been archived, and are available to the public as well as to researchers. For the purposes of this study, a consolidated data file compiled by the RAND corporation was used for analysis (RAND HRS Data, 2014).

Procedure

In this study, data collected every two years (beginning in 1992), from American older adults, will be utilized. The HRS dataset includes the measurements of cognitive functioning collected two years before cancer diagnosis, and then three times after diagnosis, with two years between each of the collection points. Also measured are treatment type received, demographic factors, depressive symptoms, health and activities of daily living (ADLs).

The selection criteria for participants for this study were answers of "yes," they had not previously reported a cancer diagnosis and "yes," they had developed cancer since the most recent interview. Participants were not excluded from the analysis if they did not report information on the type of cancer treatment received. Data were collected using a floating baseline methodology (e.g. Burton, Galatzer-Levy, & Bonanno, 2014). A floating baseline methodology entails anchoring participants' data to the year of cancer diagnosis, so that comparisons can be made among individuals who were diagnosed in different years. Only individuals who were still alive four years after their initial cancer diagnosis, and had completed cognitive testing as part of the HRS data collection in at least three interviews, were included in the analyses, both to identify long-term outcomes among cancer survivors, and for purposes of optimal model convergence.

Based on the above selection criteria, 403 participants were included in the analyses (see Table 1 for demographic characteristics). Participants consisted of 52.3% males and 47.1% females, with 86.6% identifying as Caucasian, 12.4% as African American, and 1.0% as of another race/ethnicity. Mean age of the sample at diagnosis was 76.15 years (SD = 8.0), with an average of 11.51 years of education completed (SD = 3.64). At the time of diagnosis, 57.1% of participants were married, 5.2% were divorced, 30.3% were widowed, and 7.4% endorsed a

different relationship status such as partnered or separated. Data about non-housing financial assets post-diagnosis were collected at each wave, and are reported in Table 1. Of the sample, 37.7% reported having less than $10,000 in assets, 30.8% reported having between 10,000 and 100,000, and 28.3% reported having more than 100,000 in non-housing financial assets at the time point immediately following diagnosis.

Measures

Cancer status. At each wave of data collection, participants were asked whether they had a diagnosis of cancer that they had not had in the previous wave of data collection. Data collected for cancer status was based on an individual answering "yes" to the question of whether they had developed cancer since their most recent interview, and had no prior history of cancer.

Treatment type. If a participant responded "yes" to the question about having been diagnosed with cancer since the previous wave of data collection, they were asked subsequent questions about treatment regimen, including whether they received chemotherapy, radiation, surgery or other. These variables were dummy coded for purposes of analysis, so that those who had treatment data available were either coded as "1" for answering "yes" to receiving a particular treatment, or "0" for "no." The three treatment types coded were chemotherapy, radiation and surgery. Of the 450 participants, treatment data were available for 235, with 46.8% of the treatment subsample reporting exclusively receiving chemotherapy, 32.3% receiving surgery, and 20.8% reporting that they received radiation.

Individual characteristic variables. Gender was measured in this study as a dichotomous variable, either female ("1") or male ("0"). Race data were also used, specifically whether the participants were White/non-Hispanic ("1"), Black ("2"), or Hispanic ("3") - the three major

racial groups sampled in the HRS. Age at cancer onset was calculated, as well the highest level of education completed in number of years (among other demographic variables reported in Table 1).

Cognitive functioning. For cognitive functioning, a measure was chosen to capture the common complaints associated with chemotherapy – specifically attention, working memory and long-term verbal memory. The Health and Retirement Study (HRS) reports a composite variable of both immediate and delayed recalled trials of a memory task, in which participants were asked to remember a list of unrelated nouns presented to them verbally (10 words to be recalled immediately after stimulus presentation, and then again 30 minutes later). This variable is called "total recall," and ranges from 0-20 (10 possible points for words recalled in the immediate trial, and 10 possible points for words recalled in the delay). This task measures attention and working memory, in addition to memory storage and retrieval. In this sample, prior to diagnosis, there was a mean total recall score of 8.97 (SD = 3.64). After diagnosis, the sample had a mean total recall score of 8.58 (SD = 3.42).

Though some have argued that a full neuropsychological testing battery is needed to assess cognitive performance (Vardy, Rourke, & Tannock, 2007), it is not possible for studies like the HRS due to time constraints and resources. Additionally, research has shown that a limited battery with fewer, more targeted assessments, such as the verbal memory test used in this study, are just as effective at assessing changes in cognitive functioning over time (Freeman & Broshek, 2002; Taylor & Heaton, 2001).

Depression. The HRS utilized an abbreviated 8-item version of the Center for Epidemiologic Studies – Depression scale (CES-D), asking participants whether they experienced any of 8 symptoms (yes or no) during the previous week (such as "I could not get

going" and "I felt depressed"). This scale has shown high internal consistency and construct validity (Radloff, 1977), and Cronbach's alphas of .80 and above (Kohout, Berkman, Evans, & Cornoni-Huntley, 1993). In the current study, CES-D scores had an alpha of .81. Prior to diagnosis, the mean depression score in the sample was 1.34 (*SD* = 1.80). After diagnosis, the mean depression score was 1.83 (*SD* = 2.03). As the clinical cutoff for this short form of the CES-D is a score of 4 (Steffick, 2000), the sample was well below the clinical level for depression overall at both time periods.

Self-reported health. Subjective health status data were collected at each time point by asking participants to rate their overall health on a 5-point scale ranging from 1=excellent to 5=poor. These subjective health ratings have been found to be reliably consistent predictors of mortality (Idler & Benyamini, 1997). Before diagnosis, the mean health score was 2.91 (*SD* = 1.11), with a mean score of 3.52 (*SD* = 1.05) after diagnosis.

Activities of daily living (ADLs). Activities of daily living (ADLs) were defined in the HRS in several ways, for example being able to walk one block, to stand up after sitting without help, dress oneself, and care for personal hygiene. After these ADLs were assessed individually, a composite measure of difficulty with ADLs was collected, asking participants to rate their difficulty with these activities on a scale from 0=no difficulty to 5=extreme difficulty. When assessed at the time point prior to diagnosis, a mean of 0.35 (*SD* = 0.85) was reported, with a mean of 0.47 (*SD* = 0.99) at the time shortly after diagnosis.

Optimism about future outcomes. Participants were asked about the probability of future outcomes regarding personal, economic and health events. These included such questions as whether they expected to "live to be 75 or more," "live to be 85 or more," "see another economic depression," "leave an inheritance," and others. The questions were asked on a scale of

0=absolutely no chance to 10=absolutely certain, and subsequently multiplied by 10 so as to have a probability distribution ranging from 0 to 100%. In many studies, this measure has been used as a proxy for optimism about the future (e.g. Galatzer-Levy & Bonanno, 2014). Alhough data based on this measure were only collected in early waves of the HRS, there were subsequent data for the preliminary analyses. Prior to diagnosis, the self-rated probability of living to the age of 75 was an average of 64.51 out of 100 (*SD* = 29.42), and the probability of living to 85 yielded a mean of 43.14 out of 100 (*SD* = 33.45). After diagnosis, the self-rated probability of living to 75 had a mean of 56.98 out of 100 (*SD* = 30.97), and the probability of living to 85 averaged 36.91 out of 100 (*SD* = 32.76). Because the mean age in the sample was over 75, self-rated probability of living to 85 or more was utilized in subsequent analyses, as it was a more relevant measure for most participants based on their age.

Other health behaviors. Data about other health behaviors relevant to cognition were also collected for analysis. These included frequency of vigorous exercise, on 5-point scales of 3+ times per week, 1-2 times per week, 1-2 times per month, less than 1 time per month or never. Prior to diagnosis, 32.1% of the sample reported engaging in vigorous exercise nearly every day, and 65.2% reported that they "never" engage in vigorous exercise. Following diagnosis, 24.8% reported nearly daily vigorous exercise, while 71.5% reported that they never engage in vigorous exercise.

Drinking and smoking behaviors were also reported. Prior to diagnosis, 15.9% of the sample reported that they were currently smoking, while 83.6% said they were not. After diagnosis, 10.2% of the sample reported smoking currently, while 89.8% denied current smoking. The average number of days per week alcohol was consumed in the sample prior to diagnosis was 1.28 (*SD* = 2.26), with an average 0.78 (*SD* = 1.63) drinks consumed on reported

drinking days. The average number of days per week participants reported drinking alcohol after diagnosis was 1.08 (*SD* = 2.15), with the average number of drinks consumed on those days 0.57 (*SD* = 1.27).

Mortality. The HRS utilized information from the National Death Index to indicate whether a participant had died at a given point. For the purpose of the current study, a dummy-coded variable was constructed to indicate mortality beyond the last measured time point (four years after diagnosis). That is, whether a participant had died by the next data collection time, between 4 and 6 years after cancer diagnosed (since the participant was still alive 4 years after diagnosis, and the next interview took place 2 years later). Information about cause of death was not available for this sample. For purposes of the analyses, the primary sample consisted of those who were still alive 4 years after diagnosis.

Please see Table 2 for descriptive statistics of study variables prior to cancer diagnosis, and Table 3 for descriptive statistics of study variables (including treatment variables) at the time after cancer diagnosis.

Data Analytic Plan

Descriptive statistics for demographic variables as well as for study variables were collected prior to diagnosis, as well as immediately following diagnosis. Correlation coefficients were calculated for all variables of interest at both pre- and post-diagnosis time points, as well.

Following the collection of descriptive statistics, a Latent Class Growth Analysis (LCGA) approach was utilized to identify the best fitting model of cognitive functioning trajectories over the course of six years (from pre-diagnosis to four years after diagnosis). A floating baseline methodology was used in order to anchor each participant's trajectory to his or her year of cancer diagnosis, so that time 1 (T1) was measured two years prior to cancer

diagnosis, time 2 (T2) indicated cancer was diagnosed since the previous interview, and time points 3 (T3) and 4 (T4) were two and four years after the post-diagnosis time point, respectively. Thus, the trajectories of cognitive functioning in response to cancer diagnosis could be compared across participants, though they may have occurred in different calendar years.

The Mplus statistical program then seeks to fit the best model of trajectories of cognitive functioning to the data, comparing increasing numbers of classes (trajectories) over the course of several analyses, until the best-fitting unconditional model was identified. The best-fitting unconditional model for the data was based on a number of numerical decision points (fit statistics such as entropy and the Akaike Information Criteria), and the number of classes that were theoretically most parsimonious (Lubke & Muthen, 2005).

Once the best-fitting unconditional model (number of latent classes of cognitive functioning) was found, several conditional models were analyzed, where covariates of membership in the classes of cognitive functioning were analyzed. These separate conditional models assessed which demographic, psychological, and health variables predicted a participant's membership in a particular trajectory of cognitive functioning.

Of particular relevance to the main hypothesis of this study was a conditional model investigating whether chemotherapy predicted membership in any of the classes of cognitive functioning (when compared to treatment with surgery and radiation). Additionally, logistic regression analyses were run to assess the impact of demographic variables on type of treatment received. Conditional models analyzing depression both before and at diagnosis, self-reported health and self-rated probability of living to the age of 85 prior to diagnosis, and ADLs at diagnosis, were also investigated. Possible demographic predictors of cognitive class

membership, such as age, gender, level of education, and financial status after diagnosis were assessed.

Finally, because this is a sample of older adults, and cognitive status (particularly on a variable like total recall) is expected to decline somewhat with age (Li, Lindenberger, & Sikström, 2001), a known class analysis was run which stratified the sample into two age groups; under the age of 80 and age 81 and over, in order to assess possible trajectory and covariate predictor differences among these age groups.

Results

Hypothesized risk and protective factors (prior to diagnosis)

Correlations among potential risk and protective factors related to total recall, as well as demographic and outcome variables collected in the wave prior to cancer diagnosis, are reported in Table 4. Race and education were significantly related to total recall, with individuals of minority status and those with fewer years of education manifesting lower recall. Additionally, poorer self-reported health and more difficulty with ADLs were significantly associated with lower recall. A higher self-rated probability of living to the age of 85 was significantly correlated with better recall, as was better self-rated memory status. Depressive symptoms were also significantly associated with total recall prior to cancer diagnosis, with more symptoms related to lower recall.

Hypothesized risk and protective factors (after diagnosis)

Correlations among hypothesized risk factors, demographic and outcome variables in the wave immediately following diagnosis are reported in Table 5. Similar to the pre-diagnosis wave, race and education were significantly associated with total recall, with minority status and fewer years of education associated with lower cognitive functioning. Additionally, gender and

age at diagnosis were significantly correlated with total recall in this wave, with male gender and older age at diagnosis associated with lower cognitive functioning. Self-reported health, self-reported memory and finances were also significantly related to total recall, with poorer health, memory and fewer financial assets associated with lower cognitive functioning. More symptoms of depression were also significantly associated with lower cognitive functioning in this wave.

Of the outcome variables added to the correlation matrix after diagnosis, treatment with chemotherapy was significantly associated with higher cognitive functioning. Neither treatment with surgery or with radiation was associated with total recall. Difficulty with activities of daily living post-diagnosis was also significantly correlated with lower cognitive functioning. Those measures significantly related to total recall were subsequently analyzed in the latent growth curve analysis (LCGA) conditional models.

Comparison of study variables before and after diagnosis

A series of paired-sample t-tests were run in order to investigate whether study variables of interest differed between the time prior to diagnosis and the data collection point after diagnosis. Depressive symptoms were significantly worse after diagnosis than prior to diagnosis in this sample (t = -4.82, p<.001). Self-reported health was also significantly worse after diagnosis than before diagnosis (t = -11.24, p<.001). When investigating differences in difficulty with ADLs from pre- to post-diagnosis, a significant increase in reported difficulty was found (t = -2.79, p<.001). There was no significant difference in self-rated probability of living to the age of 85 from pre- to post-diagnosis (t = -1.20, p=.23).

Regarding the difference in total recall scores over time (between four years prior to diagnosis and four years after diagnosis at two-year data collection intervals), a series of paired-sample t-tests was performed. Total recall at two years prior to the pre-diagnosis time was not

significantly different from total recall at the pre-diagnosis time point ($t = 1.911$, $p>.05$). However, total recall after diagnosis was significantly lower than total recall prior to diagnosis ($t = 2.57$, $p<.05$). When the difference in total recall was investigated from post-diagnosis to two years later, there was a significant difference ($t = 2.14$, $p<.05$), with total recall at the later time point lower than at the post-diagnosis time. Total recall continued to be significantly lower four years after diagnosis when compared to two years after diagnosis ($t = 2.91$, $p<.01$). In the sample overall, total recall decreased significantly in every time window after the initial diagnosis.

Unconditional model

A latent class growth analysis (LCGA) approach was performed using Mplus version 7.0 (Muthen & Muthen, 1998-2010), in order to identify the optimal number of trajectories of cognitive functioning for the sample, using total recall as the dependent variable to be modeled. A series of models with an increasing number of possible classes (or, latent populations of cognitive functioning) were compared - categorizing participants into one, two, and three classes. For purposes of model identification and convergence, the intercept, slope and quadratic terms were fixed for all analyses (Jung & Wickrama, 2008).

In order to identify the number of classes that best fit the data, several fit criteria were assessed. These fit criteria were the Akaike information criteria (AIC), the regular and sample-size-adjusted Bayesian information criterions (BIC and ssBIC), entropy values, Lo-Mendell-Rubin test (LMR), and bootstrap likelihood-ratio tests (BLRT). Values of these fit criteria are presented in Table 6, presented in order of number of classes. In order to identify the best-fitting model, values of the above-mentioned fit statistics were taken into account, along with theoretical considerations and parsimony of interpretation (Lubke & Muthen, 2005). Investigation of the models began at one class, and increased in class number until the optimal

number of classes was identified. As the models increased from one to two classes, and again from two to three classes, improvements were seen in all fit criteria. However, a four class model failed to show a decrease in the AIC and BIC (which is the hallmark of improved model fit), and a non-significant bootstrap likelihood-ratio test. Additionally, the four-class model split the classes so that the fourth and smallest class was made of less than 2% of the sample, which is neither a parsimonious solution nor does it add any theoretical clarity. Thus, a three-class model of total recall over time was found to be the best-fitting model (see Figure 1).

The largest of the three classes was the Middle Recall Class (52% of the sample), with an average stable total recall score across all time points. This class was characterized by a median initial intercept (b = 9.54, *S.E.* = 0.29, p<.001), a non-significant negative slope (b = -0.52, *S.E.* = 0.31, p=.09), and a non-significant quadratic parameter (b = -0.01, *S.E.* = 0.09, p=.92). The second, and second largest of the three classes was the Lower Recall Class (30% of the sample), with a lower intercept and lower recall over time. This class was characterized by a low initial intercept (b = 5.52, *S.E.* = 0.37, p<.001), a non-significant negative slope (b = -0.43, *S.E.* = 0.42, p=.31), and a non-significant quadratic parameter (b = 0.01, *S.E.* = 0.13, p=.97). The third, and smallest class, was the High Recall Class, characterized by a high initial intercept (b = 12.90, *S.E.* = 0.59, p<.001) and continued high recall across time points. This class was also characterized by a non-significant (though slightly positive) slope (b = 0.02, *S.E.* = 0.54, p=.97), and a non-significant quadratic parameter (b = -0.12, *S.E.* = 0.16, p=.47). These three classes of cognitive functioning are presented in Figure 1.

Conditional model with treatment type as a covariate

In order to assess the impact of receiving chemotherapy treatment on cognitive functioning, compared to receiving surgery or radiation treatment, the three-class solution was

run as a conditional model using treatment type as a covariate. In order to proceed with interpretation of this conditional analysis, fit statistics such as Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), and entropy values were investigated for similarity to the unconditional model, as well as the retention of the original three classes. Since these fit criteria values and three class proportions were comparable to the unconditional model, the conditional model results for treatment type as covariate were analyzed, with results reported in Table 7.

For the first set of analyses, the High Recall Class was used as the comparison group. Compared to the High Recall Class, individuals in both the Middle Recall and Low Recall Classes were significantly less likely to have received treatment with chemotherapy. Treatment with surgery and treatment with radiation did not predict membership in either the Middle or the Low Recall Class when compared to the High Recall class.

Next, the Low Recall class was used as the comparison group to investigate probability of class membership by treatment type. When compared to the Low Recall Class, participants in the High Recall Class were significantly more likely to have received treatment with chemotherapy. There was no difference in likelihood of class membership for treatment with surgery or radiation. None of the treatment type differentiated membership between the Low Recall and Middle Recall Classes.

Logistic regression using demographics to predict treatment type

In order to better understand the finding that treatment with chemotherapy predicted membership in the High Recall class, logistic regression analyses were performed to determine whether demographic characteristics predicted receipt of a particular treatment type. The demographics added into the model as possible predictors of treatment type were finances at onset of illness, education, race, and age at onset.

When predicting treatment with radiation, the model including all demographic variables only explained 6% of the variance above the intercept model. The only significant predictor of receiving radiation was age at onset ($\beta = .939$, $p<.01$), with younger individuals more likely to receive radiation than older individuals (see Table 8). Finances, education, and race, did not predict receipt of radiation therapy.

The next logistic regression was run to assess demographic predictors of treatment with surgery (see Table 9). The full model only predicted 4% of the variance in treatment with surgery above the intercept model, and none of the demographic variables investigated significantly predicted treatment with surgery.

Finally, a logistic regression was used to analyze predictors of treatment with chemotherapy (see Table 10). In contrast to the other two models, demographic factors predicted more variance in receipt of chemotherapy (11%), with younger age significantly increasing the likelihood of receiving chemotherapy ($\beta = .921$, $p<.001$).

Conditional model with depression as a covariate

In order to assess the impact of depressive symptoms (both pre-diagnosis and following diagnosis) on cognitive functioning, the three-class solution was run as a conditional model using depression as a covariate. Similar to the conditional model described above, fit statistics and class proportions were determined to be in line with the unconditional model before proceeding with interpretation of this conditional model. Since these criteria were met, the conditional model results for depression as covariate were analyzed, with results reported in Table 11.

When compared to the Low Recall Class, pre-diagnosis depression did not significantly predict membership in either the Middle Recall or High Recall classes. However, fewer depressive symptoms post diagnosis did significantly predict membership in both the Middle

Recall and High Recall Classes, when compared to the Low Recall Class. When compared to the Middle Recall Class, pre-diagnosis depression was also not predictive of membership in either the Low or High Recall Classes. Those in the Low Recall Class had significantly more depressive symptoms post-diagnosis than those in the Middle Recall Class.

Conditional model with health factors as covariates

A conditional model was investigated, with self-reported health pre-diagnosis, reported probability of living to the age of 85 pre-diagnosis, and ADLs after diagnosis, entered as covariate predictors of class membership. Results from these analyses are reported in Table 12, since this model demonstrated adequate fit and retention of class proportions from the unconditional model.

When compared to the High Recall Class, individuals in the Middle Recall Class reported a significantly lower probability of living to the age of 85 pre-diagnosis. There were no differences between the Middle Recall and High Recall classes on self-reported heath pre-diagnosis, or difficulty with ADLs after diagnosis. Individuals in the Low Recall Class reported a significantly lower probability of living to the age of 85 pre-diagnosis as well, and reported significantly more difficulty with ADLs post-diagnosis than did those in the High Recall Class.

When compared to the Middle Recall Class, individuals in the High Recall Class reported a significantly higher probability of living to the age of 85 (assessed pre-diagnosis). Neither self-reported health pre-diagnosis, nor difficulty with ADLs post-diagnosis, differentiated the Middle and High Recall Classes. When the Low Recall Class was compared to the Middle Recall Class, these individuals were found to have significantly more difficulty with ADLs post-diagnosis.

Conditional model with demographic factors as covariates

In order to investigate demographic predictors of class membership, a conditional model was run using age, gender, education level, financial assets, and marital status as covariates (see Table 13). To aid in model convergence, age and financial assets were standardized before they were entered into the regression model. Of note, age at diagnosis, non-housing financial assets at diagnosis, and marital status at diagnosis were utilized in this model.

In the first analysis, the High Recall Class was used as the comparison class. Compared to the High Recall Class, both the Middle and Low Recall Classes were significantly older, more likely to be male, and to have a lower level of education. There were no differences in class membership based on financial assets between the Middle and Low Recall Classes and the High Recall comparison class. The Low Recall Class was significantly less likely to be married at the time of diagnosis than the Higher Recall Class. There was no difference in marital status between the Middle and High Recall Classes.

Subsequently, when compared to the Low Recall Class, individuals in the High Recall Class were significantly more likely to be younger, female, have a higher level of education, and have been married at the time of diagnosis. Those in the Middle Recall Class were significantly older, and have a higher level of education than those in the Low Class. There was no difference between classes based on financial assets in this model. Additionally, the Low and Middle Recall Classes did not differ based on gender or marital status at diagnosis.

Conditional model with known class (stratified by age)

To examine the effects of age on the trajectories of cognition, the chosen three-class solution from the unconditional model was analyzed using age as a known class variable. In order to do this, the sample was split into two groups- those under the age of 80 at diagnosis

(62.5% of the sample) and those over the age of 80 at diagnosis (37.5% of the sample). The results of this analyses indicated the same three classes among participants under the age of 80 as those over the age of 80, with entropy of .847 indicating the model continued to adequately fit the data when the known class variable was included (see Figure 2).

In the under 80 group, 17.5% were classified into the High Recall Class, 57.5% into the Middle Recall Class, and 25% were classified into the Low Recall Class. In the over 80 group, 13.2% were classified into the High Recall Class, 49.3% were classified in to the Middle Recall Class, and 37.5% were classified into the Low Recall Class.

Multinomial regression analyses were conducted, testing difference in likelihood of class membership based on the known class variable, using the High Recall Class as the reference class. Results indicated no difference in membership likelihood for the Low Recall Class (b=-0.55, *S.E.*=0.39) when compared with the High Recall Class. However, being over the age of 80 made it significantly more likely to belong to the Middle Recall Class than the High Recall Class (b=2.22, *S.E.*=0.48, p<.01). Finally, parameter estimates (intercept, slope and quadratic) did not differ significantly between the two age groups for any of the cognitive classes.

Conditional model of treatment type by age interaction

In order to further investigate the finding that individuals treated with chemotherapy were more likely to belong to the High Recall Class, another conditional model for treatment type was run, this time entering age group x treatment type as an interaction term. In this model, the High Recall Class was again used as the reference class. When the interaction terms were included in this analysis, the only significant interactions were between treatment with chemotherapy and age group. That is, when compared with the High Recall Class, individuals in the Middle Recall Class who were treated with chemotherapy were significantly more likely to be under the age of

80 (b=-1.92, $S.E.$=0.96, p<.05). There were no interactions between age group and either treatment with surgery or radiation on total recall class.

Of note, when age group was entered into this model in addition to treatment type and the age x treatment type interaction terms, chemotherapy was no longer a significant predictor of membership in the High Recall Class. That is, the interaction between age and treatment with chemotherapy appears to have been driving the previous finding of increased membership likelihood in the High Recall Class after treatment with chemotherapy.

Discussion

Results of the present study indicate that, among older adults with cancer, demographic, treatment, psychological and other health factors are associated with cognitive functioning over time. When the cognitive functioning of this sample was investigated over the course of six years, three fairly stable trajectories of total recall were identified (High Recall, Middle Recall and Low Recall, with Middle Recall as the modal trajectory). In contrast to a significant body of research on cognitive impairment associated with chemotherapy (e.g. Ahles et al., 2002; Vardy & Tannock, 2007), this study did not evidence an association between treatment with chemotherapy and lower cognitive functioning over time. In fact, treatment with chemotherapy initially appeared to be related to higher functioning cognition trajectories, though after further analysis, this relationship is moderated by age of the individual undergoing treatment. In contrast to the treatment factors investigated, depressive symptoms post-diagnosis, demographic factors such as age and education, activities of daily living and self-rated probably of living to the age of 85 did significantly predict membership in certain cognitive classes.

In light of these findings, it is important to understand which factors put older adults diagnosed with cancer at risk for negative cognitive outcomes, as well as which factors are

protective. Additionally, the results of this study have important implications for early intervention and health care policy as it relates to older adults, as well as provide information about possible outcomes based on a variety of factors at pre- and post-diagnosis. This line of inquiry is especially important as the population ages in greater proportion, and rates of cancer incidence and cancer survival increase. Understanding the long-term impact of cancer and its treatment on cognitive functioning as it relates to many other psychological, health and quality of life factors, will hopefully aid in the ability of older adult cancer survivors to live out their lives with health and greater meaning – an outcome that greatly benefits society as a whole.

Identifying risk and protective factors

Treatment factors. From the results of this study, it appears that undergoing a particular cancer treatment (radiation, chemotherapy or surgery) does not impede cognitive functioning over the long run (specifically, none of the treatments listed predicted membership in the Low Recall Class). In fact, a surprising finding in this study was that treatment with chemotherapy predicted membership in the *High* Recall Class. In order to better understand the mechanisms behind this association, further analyses were undertaken. Since it seemed possible that there could be other variables, such as socioeconomic status and race, that could be highly correlated with treatment type received and have implications for cognitive functioning, logistic regression analyses using demographic variables to predict treatment type were run. In these analyses, only age emerged as a predictor of treatment type (with younger age predicting treatment with both chemotherapy and radiation, but not surgery). Since younger age was a significant predictor of treatment, the conditional model of treatment type was re-analyzed, with age (stratified into under and over the age of 80) and age by treatment type interactions added as possible predictors of cognitive class.

When these additional covariates were added, several clarifying findings emerged. First, treatment with chemotherapy was no longer associated with membership in the High Recall Class. However, there was a significant age by treatment type interaction, showing that individuals in the High and Middle Recall Classes who had received treatment with chemotherapy were significantly more likely to be under the age of 80. That is, younger individuals were more likely to have received this treatment than older individuals to begin with (as seen in the logistic regression findings), and they were more likely to have been in the High and Middle Recall Classes. Thus, it appears that the original finding that chemotherapy improves likelihood of better cognitive functioning over time is at least somewhat confounded by age – indicating that younger age is a protective factor against cognitive decline in the long term, regardless of whether chemotherapy treatment is used.

This finding is interesting for several reasons. While it is intuitive and well documented that some cognitive decline is natural with age (Li, Lindenberger, & Sikström, 2001), it does not explain the age by chemotherapy interaction. Indeed, the vast majority of research on CICI has been conducted in middle-aged adults younger than the "young" sample studied here (aged 62-80), with findings still showing cognitive difficulties (Vardy & Tannock, 2007). However, there have also been many studies failing to show a link between chemotherapy treatment and cognitive decline (e.g. Donovan et al., 2005; Jenkins et al., 2006; Keating, Nørredam, Landrum, Huskamp, & Meara, 2005; Porter, 2013; Shaffer et al., 2012).

It is certainly possible that younger individuals are more likely to receive chemotherapy in general based on ageist perceptions that older individuals are less likely to survive their cancer, or tolerate the course of treatment without serious detriment to their health (Bond et al., 2003; Janssen-Heijnen et al., 2007; Peake, Thompson, Lowe & Pearson, 2003). Another possible

explanation is that those younger individuals in the sample have been diagnosed early, and are thus likely to have better outcomes on a variety of cognitive and health variables post-treatment regardless, especially as treatments advance and rates of survival improve (Siegel et al., 2012). Additionally, there may be a difference in treatment type by cancer type for these individuals not able to be captured in the present study due to limited data on these factors, although a previous study utilizing the HRS dataset failed to find an association among cancer type, treatment type, and depression (Burton, Bonanno, & Galatzer-Levy, 2014). Whatever the reasons, the results of the present study indicate that for "younger" older adults, treatment with chemotherapy as well as their age bode well for positive cognitive sequelae over time.

Importantly, when age was added as a covariate, chemotherapy (and neither of the other cancer treatments investigated) did not predict membership in any of the cognitive classes identified in this study. Though the interview time points were widely spaced, making a more nuanced investigation of real-time cognitive side effects during treatment logistically difficult (and could certainly explain the difference among this study's findings and those studies exploring cognitive decline during and immediately following chemotherapy treatment), it is hopeful that in the long term, among cancer survivors, chemotherapy did not be found to increase the likelihood of negative cognitive outcomes, even if some cognitive side effects of treatment were initially experienced and not captured in this dataset. Indeed, Schagen et al. (2002) noted no enduring cognitive symptoms after several years in a sample that had previously shown significant problems associated with their treatment. Though it is impossible to say whether such symptoms may have been experienced in this sample, the long-term lack of association between chemotherapy and negative cognitive outcomes, even in an older sample

potentially more susceptible to such changes (Puts et al., 2012), is both noteworthy and heartening.

Demographic factors. Many studies have shown that demographic factors are associated with health and cognitive outcomes across the lifespan, and among older adults in particular (e.g. Proust-Lima et al., 2008; Rabbitt, Donlan, Watson, McInnes, & Bent, 1995). Theoretical concepts like cognitive reserve postulate that protective factors like intelligence and level of education help bolster older individuals against experiencing cognitive decline, even along with neurodegenerative processes (Stern, 2003).

In line with these findings, results of this study showed that compared with the Low Recall Class, individuals in the High Recall Class were more likely to be younger, female, have more years of education, and be married. Compared to the Low Recall Class, those in the Middle Recall Class were more likely to be younger, and have more years of education.

Education level as a buffer against cognitive decline has been well documented, both in the cognitive reserve literature (Stern, 2009), and in its potential association with intelligence and career choices, all of which have been shown to bolster cognitive functioning in late life (Whalley, Deary, Appleton, & Starr, 2004). Research has also shown bolstering of "neural reserve" in more educated individuals with the mediation of structural changes in the hippocampus, another potential explanation for this association (Piras, Cherubini, Caltagirone, & Spalletta, 2011).

Because of some expected minimal cognitive decline associated with age, as well as the possibility that the older individuals in this sample may have also begun to be affected by neurodegenerative processes in addition to the sequelae of cancer (Bäckman, Jones, Berger, Laukka, & Small, 2005), the association between younger age and the Middle and High Recall

Classes makes sense. In contrast to the findings in the present study, women have been shown to have greater decline in cognitive outcomes in late life than men, possibly related to a longer life expectancy and thus more health problems that might affect cognition among older women (Karlamangla et al., 2009).

Also of interest was the likelihood of being in the High Recall Class if married at diagnosis, and the accompanying likelihood of being in the Low Recall Class if single at diagnosis. There are several possible ways to understand this finding. Firstly, having a partner during an illness has been shown to increase positive outcomes (Pienta, Hayward, & Jenkins, 2000), which could very well include and affect cognitive functioning for a variety of reasons ranging from emotional support to help with proper medication adherence. Additionally, individuals who are married in later life have many other positive psychosocial and health benefits, including lower depression (Schoevers et al., 2000) and more social and intellectual stimulation (Fratiglioni, Paillard-Borg, & Winblad, 2004), all possible protective factors against lower cognitive functioning among older adults.

Finally, it is noteworthy that no association was found between financial status at the onset of cancer and cognitive functioning trajectory. In much of the literature on health outcomes in late life, individuals of lower socioeconomic status have been shown to be at particular risk for a host of negative health and psychosocial outcomes due to lack of resources and access to quality healthcare (Seeman et al., 2004). It's possible that, in the present investigation, other factors like education and general health accounted for a greater proportion of the variance in cognitive status, or that possible associations between cognitive and socioeconomic status would have preceded the first data collection point. That is, an individual whose finances and access to

resources affected their cognitive functioning over time may have been affected across the lifespan in ways not captured by the variables in this study.

Depressive symptoms and cognition. The literature on depression and cognition in late life has found that depressive symptoms are generally associated with cognitive deficit (Butters et al., 2000). In particular, cognitive deficits that mimic cognitive symptoms associated both with cancer and with cancer treatment (Silberfarb, Philibert, & Levine, 1980). Hence, it was of interest to explore whether depressive symptoms would predict a degree of total recall by predicting membership in a particular class of cognitive functioning. To address questions of the relationship between depressive symptoms and cognitive functioning, depressive symptoms prior to a cancer diagnosis were explored as a predictor of membership in a particular cognitive functioning class. Unlike other studies, which have provided evidence of the relationship between depression and cognitive dysfunction in later life (McClintock, Husain, Greer, & Cullum, 2010), pre-diagnosis depressive symptoms did not predict membership in any of the three cognition classes in this study. However, the fact that subclinical depression was found in this sample may account for the difference. That is, it is possible that a clinical population with greater depressive symptom severity may have showed a greater association between depressive symptoms prior to diagnosis and cognitive outcome.

In contrast, post-diagnosis depressive symptoms did differentially predict membership in the cognitive trajectories identified in this study. Specifically, individuals in the Low Recall class were more likely to have a higher rate of depressive symptoms following a cancer diagnosis than did individuals in either the Middle or High Recall classes. Interestingly, pre-diagnosis depressive symptoms did not differentiate among the recall classes. It is also possible that for this

sample, having middle or higher levels of cognitive functioning may be protective against depressive symptoms following a cancer diagnosis.

This finding has important implications for intervention, and identifying individuals potentially at risk for worse cognitive outcomes following cancer treatment, and prioritizing access to treatment for those individuals. Because it has been shown that treatment of depression in late life also improves cognitive performance (Butters et al., 2000), being able to identify individuals who show symptoms of depression immediately following diagnosis, and beginning treatment immediately, may protect against cognitive decline, and offer other health benefits as well. Additionally, the knowledge that post-diagnosis best predicts lower cognitive functioning will allow health care professionals to target the most optimal time for intervention.

Physical health and functioning factors. In addition to the psychological, demographic and treatment variables described above, other physical health and functioning factors were found to affect membership in particular cognitive classes. Specifically, more difficulty with activities of daily living post-diagnosis and lower self-rated probability of living to age 85 pre-diagnosis predicted membership in the Low Recall Class, compared to the High Recall Class. Self-rated health was not predictive of class membership in this study.

Activities of daily living have been associated with a variety of health and cognitive outcomes among older adults (McGuire, Ford, & Ajani, 2006), as well as a reliable barometer for general health status (Freedman et al., 2013). Indeed, in a study examining various predictors of worsening cognitive trajectories among older adults, ADLs more accurately tracked a worsening trajectory than number/length of hospitalizations (Han, Gil, Jones, & Allore, 2015). Though these associations have been well documented and were replicated in this study, the fact of lower functioning immediately after diagnosis affecting cognitive functioning years later indicates this

is a critical period for intervention and bolstering of ADLs among newly diagnosed older adults. It is possible that encouraging physical exercise in moderation and recommending caregivers to allow ill individuals to perform ADLs on their own, a potentially difficult task for someone coping with cancer and those taking care of them, could help avoid some negative cognitive outcomes (e.g. Wolinsky et al., 2011). It is possible that psychoeducation for family members and caregivers could help increase understanding and implementation of beneficial regimens to improve functioning, or at least ensure ADLs remain stable.

The self-rated probability of living to the age of 85, when measured two years prior to diagnosis, was also predictive of membership in the High Recall Class. Though potentially related to other psychological and sociodemographic factors, this measure of perceiving longevity and optimism about longevity appears to confer protective benefits. The degree to which such optimism may protect against cognitive decline even when dealing with a major illness has been found among heart attack survivors, who are more likely to survive for years after the health crisis (Galatzer-Levy & Bonanno, 2014). In line with this finding, a study conducted by Levy, Ashman, and Dror (2000) found that older adults who did not have hope for longevity were more likely to have negative health outcomes that affected their mortality (though it is possible this finding could work both ways). Longitudinal research has also been done in this area, highlighting the detrimental physical health consequences of negative health views, in addition to psychological consequences such as feeling a lack of control over one's health and future (Wurm, Tesch-Römer, & Tomasik, 2007). These examples, coupled with the findings in this study, show the potential for optimism to be related to important and concrete benefits for cognition and health among older adults.

Recommendations for health care professionals and others

The findings from this study provide valuable information about risk and protective factors related to cognitive functioning among older adults with cancer, as well as optimal timing for effective interventions. Based on these results, there are several recommendations that can be made to health care providers who work with this population, as well as to family members and caregivers, to best support optimal functioning and sustaining a positive and meaningful quality of life in remission.

Since there were many factors, across domains, that were found to affect cognitive functioning over time, it will be important for health care professionals to keep in mind, first and foremost, that cognition in older adults with cancer is multifaceted, and cannot be addressed in a vacuum. Taking a more holistic approach to physical health that includes psychological, emotional, basic functioning and other health variables will help doctors and other health care providers best address concerns about cognitive functioning as it relates to other important factors in a person's life, as well as their ultimate quality of life and sense of meaning. For example, inquiring about depressive symptoms, ADLs, and mindset/optimism during routine visits, in addition to frequent screening for cognitive status, will allow medical professionals to get a better sense of the interplay of psychosocial and health factors for each individual patient, so that they may recommend early and appropriate interventions based on targeted information.

Though there has been a concerted effort to address and reduce ageism among physicians, starting from medical school training (Hurria et al., 2008), there remain problematic assumptions made about the cognitive functioning and health status of older adults (Leung, LoGiudice, Schwarz, & Brand, 2011), especially when illness such as cancer is involved (Schroyen, Adam, Jerusalem, & Missotten, 2015). Educating health care providers about the

multiple contributors to lowered cognitive functioning among older adults in general and cancer patients in particular may help to refocus their efforts on intervention, greater vigilance about screening for cognitive complaints, and working with individuals and their families to address possible contributors to cognitive difficulties, such as depression (Keefe, 2016).

Hopefully, armed with this knowledge, doctors will be less likely to exclude older adults from certain treatments and clinical trials based on the perception that they won't be able to "handle them," or based on concern about altered cognitive states (Townsley, Selby, & Siu, 2005). This is especially problematic when the patient internalizes these negative beliefs, leading to increased risk for health problems and mortality (Levy, 2003). Finally, helping providers to adopt the perspective that stable to high cognitive functioning over time is the modal outcome, even after experiencing cancer and cancer treatment, will hopefully aid in enhancing positive perceptions of living well in late life, even after illness.

The results of this study in regard to the effects of chemotherapy on cognitive functioning were heartening, and diverge from much of the literature about CICI in cancer patients. Though there are some possible methodological reasons for this finding, there are other possibilities as well. Advances in oncology over the last 20 years have led to new approaches in regard to the types, doses and lengths of chemotherapy treatment, including targeted therapies based on genetic variants of certain cancers (Slamon, Romond, & Perez, 2006). These advances have also included medications that allow for greater patient tolerance of treatment regimens and fewer side effects (e.g. Cortes & Saura, 2010). Other treatments for cancer such as laparoscopic surgery (Darzi & Mackay, 2002) and targeted radiation (Baskar, Lee, Yeo, & Yeoh, 2012), as well as improved screening and early detection of these diagnoses (Brenner, Gondos, & Arndt, 2007), have also led to impressive changes, with improvement seen in the survival rates for

many cancers (Siegel et al., 2012). In light of these advances, health care professionals may not need to be quite as cautious about recommending certain treatments to older patients, especially in light of the lack of adverse consequences from chemotherapy in this study. However, it is important to note that, because of the age interaction and potentially biased survivorship sample, it is not possible to make generalizations about the reactions to chemotherapy treatment of all older adults newly diagnosed with cancer. Expecting that older individuals can live well for longer periods of time, and may not be as adversely affected by chemotherapy (particularly if they are under the age of 80 and have other protective factors against cognitive decline), may have the added benefit of widening the scope of treatments recommended, with ultimately improved outcomes.

Finally, implementation of psychoeducation for family members and caregivers around the various factors affecting cognition in older adults with cancer would be of tremendous benefit to both patients and their loved ones. Since these individuals spend the largest amount of time with the individuals affected, they can both be taught to be sensitive to important changes, and to seek intervention as needed. Also, knowledge that functioning well and maintaining a stable cognitive status over the long run is the modal response may be of emotional benefit to both patients and their families and caregivers. Such optimism may in turn provide health benefits, and may lead to higher rates of treatment, and to a greater quality of life.

Limitations and Future Directions

Though the present study adds to an understanding of the factors affecting cognition among cancer patients in late life, it is important to acknowledge its limitations. Although the Health and Retirement Study allows for access to a large sample over a long period of time, including prospective information prior to a cancer diagnosis, the data lack specificity in certain

domains. First, there is limited information about type and severity of cancer, as well as about specific cancer treatments, dosing, and other important information about the cancer itself. Though a study using the same dataset did not find associations between cancer type and the depression trajectories associated with chemotherapy (Burton, Bonanno, & Galatzer-Levy, 2014), these associations cannot be ruled out. Second, there was a long window between data collection periods (two years), so this study was unable to measure subtle cognitive changes in real time alongside treatments. Following, it is possible that individuals in this sample did experience declines in cognitive functioning related to certain treatments that were not able to be captured in the analyses performed here. It's also possible that there was a selection bias in which individuals accepted recommendations for treatment with chemotherapy, which might have influenced the results. One study showed that while there was no difference between older and younger adults in acceptance of chemotherapy in a hypothetical medical scenario, there was a difference in the willingness to accept further toxic treatment in exchange for current quality of life at later disease stages (Yellen, Cella, & Leslie, 1994), further indicating the possibility that other factors are likely influencing treatment decisions among older adults.

Third, there are inherent limitations in the use of self-report data (potential bias, omission, etc.) in relation to the health and treatment variables, as well as a lack of objective data confirming cancer and treatment status, and about difficulties with ADLs. Research on the cumulative effects of multiple health comorbidities have shown that greater allostatic load negatively affects cognition among older adults (McEwen, 2002), and therefore it is possible that other health problems experienced among the individuals in this sample might be affecting the findings. Future research would benefit from using both objective treatment data and records, as well as reports from caregivers or family members, in addition to patient self-reports.

Because this study was conducted in a unique sample of older adults who had survived cancer, it will require further research to determine whether the relationships among cancer, cognition, psychological, health and demographic factors differ for individuals who passed away before the wave two years after diagnosis. Additionally, because these data were from a much larger study with a relatively small sample of individuals from minority groups, it is unclear whether these results would be found in a study in which there was oversampling for minority status. It would also be of interest to employ measures of cognitive functioning other than those measuring immediate and delayed recall (a measure of working and long-term memory), in order to determine differences in trajectories of functioning in a wider array of cognitive functions potentially affected by cancer, cancer treatment, and normal aging. It could also be that the way cognition was measured in this study is a relatively stable measure, that is, not sensitive enough to measure small changes that may affect functioning in daily life.

Finally, this sample overall had fairly low levels of depressive symptoms, and relatively stable levels of cognitive functioning, likely due to the fact that the HRS data were not collected from a clinical sample. Certainly, the levels of depressive symptomatology in this sample of cancer survivors did not reach the levels reported in other studies, either in proportion or in severity, nor did the lack of a finding of CICI in any way mirror studies citing prevalence of this phenomenon up to 75% in some studies (Vardy & Tannock, 2007). It is possible that this sample of survivors were in better health, both physical and psychological, than those individuals in studies reporting lower functioning overall (Deimling, Kahana, Bowman, & Schaefer, 2002).

Future studies should sample in shorter intervals, use more sensitive and varied measures of cognitive functioning and other health factors in addition to objective health and treatment data (particularly taking into account health comorbidities such as diabetes and vascular risk

factors that might affect cognition, and qualitative information about decisions to undergo particular treatments), as well as attempt to assess differences between a sample who survived cancer and those who did not. Continuing to sample longitudinally to understand the relationships among these variables prospectively is advised, as it allows for the greatest control and specificity when understanding the onset, prevalence and outcomes of cognition and other psychosocial and health factors related to cancer among older adults.

Conclusions

Despite these limitations, the current study represents an important step toward understanding the various demographic, psychological, treatment and health factors that affect cognition among older adults with and surviving cancer. A longitudinal analysis was conducted in order to determine protective and risk factors associated with trajectories of cognitive functioning from before cancer diagnosis, immediately following diagnosis, and four years later. Risk factors for lower cognitive functioning included male gender, older age, fewer years of education, single marital status, post-diagnosis depressive symptoms, pre-diagnosis self-rated lower probability of living to the age of 85, and more difficulty with activities of daily living post-diagnosis. Treatment with chemotherapy did not predict membership in a lower functioning cognitive class, and in fact, when moderated by younger age, predicted membership in the higher functioning cognitive classes over time. Using this information, proposals are made for identifying individuals at greatest risk for negative cognitive sequelae at the time of diagnosis, as well as possible interventions, leading to more positive holistic outcomes for older adult cancer survivors.

Table 1. Demographic characteristics (n=403)

	Mean (SD)	Range
Age (At Diagnosis)	76.15 (8.0)	62-98
Gender		
Male	52.9%	n=213
Female	47.1%	n=190
Race		
Caucasian	86.6%	n=349
African American	12.4%	n=50
Other	1.0%	n=4
Years of Education	11.51 (3.64)	0-17
Highest Level of Education		
No Degree	33.3%	n=134
GED	4.0%	n=16
High School Diploma	29.8%	n=120
High School Equivalent	15.1%	n=61
Associates/Some College	2.7%	n=11
Bachelors Degree	8.9%	n=36
Masters/MBA	4.7%	n=19
Law Degree/MD/PhD	1.5%	n=6
Relationship Status (At Diagnosis)		
Married	57.1%	n=230
Married, Spouse Absent	0.7%	n=3
Partnered	2.2%	n=9
Separated	0.2%	n=1
Divorced	5.2%	n=21
Separated/Divorced	2.2%	n=9
Widowed	30.3%	n=122
Never Married	1.7%	n=7
Financial Assets, Non-Housing (At Diagnosis)		
<10,000	37.7%	n=152
10,000-100,000	30.8%	n=124
>100,000	28.3%	n=114
Religious Affiliation		
Protestant	62.8%	n=253
Catholic	27.8%	n=112
Jewish	3.0%	n=12
None/No Preference	4.5%	n=18
Other	1.2%	n=5

Table 2. Study variables pre-diagnosis (n=403)

	Mean (SD)	Range
Total Recall (Immediate + Delayed Recall)	8.97 (3.64)	1-20
Cognition Total Score (Mental Status + Memory)	21.50 (5.11)	5-32
Vocabulary Score	5.50 (2.11)	0-10
CES-D Depression Score	1.34 (1.80)	0-8
Self-Reported Health	2.91 (1.11)	1-5
Excellent Health	11.9%	n=48
Very Good Health	24.1%	n=97
Good Health	32.0%	n=129
Fair Health	25.6%	n=103
Poor Health	6.5%	n=26
Difficulty with Activities of Daily Living	0.35 (0.85)	0-5
Self-Reported Vigorous Exercise		
Nearly Every Day	32.1%	n=107
Never	65.2%	n=217
Currently Smoking		
Yes	15.9%	n=64
No	83.6%	n=337
Number of Days Per Week Drinking Alcohol	1.28 (2.26)	0-7
Number of Alcoholic Drinks Per Day (When Drinks)	0.78 (1.63)	0-12
Self-Rated Probability of Living Past 75	64.51 (29.42)	0-100
Self-Rated Probability of Living Past 85	43.14 (33.45)	0-100

Table 3. Study variables post-diagnosis (n=403)

	Mean (SD)	Range
Total Recall (Immediate + Delayed Recall)	8.58 (3.42)	0-20
Cognition Total Score (Mental Status + Memory)	20.95 (5.04)	6-35
Vocabulary Score	5.34 (2.14)	0-10
Received Chemotherapy	27.3%	n=110
Received Surgery	18.9%	n=76
Received Radiation	12.2%	n=49
CES-D Depression Score	1.83 (2.03)	0-8
Self-Reported Health	3.52 (1.05)	1-5
Excellent Health	4.7%	n=19
Very Good Health	10.7%	n=43
Good Health	31.0%	n=125
Fair Health	35.5%	n=143
Poor Health	18.1%	n=73
Out of Pocket Medical Expenses	6329.01 (19004.50)	0-217500
Difficulty with Activities of Daily Living	0.47 (0.99)	0-5
Self-Reported Vigorous Exercise		
Nearly Every Day	24.8%	n=100
Nearly Never	71.5%	n=288
Currently Smoking		
Yes	10.2%	n=41
No	89.8%	n=360
Number of Days Per Week Drinking Alcohol	1.08 (2.15)	0-7
Number of Alcoholic Drinks Per Day (When Drinks)	0.57 (1.27)	0-15
Self-Rated Probability of Living Past 75	56.98 (30.97)	0-100
Self-Rated Probability of Living Past 85	36.91 (32.76)	0-100

Table 4. Correlation matrix for study variables pre-diagnosis

	1	2	3	4	5	6	7	8	9	10	11
1. GENDER											
2. RACE	-.031										
3. EDUCATION	-.035	-.277**									
4. SELF-REPORTED HEALTH	.090	.098*	-.312**								
5. DIFFICULTY WITH ADLS	.035	.153**	-.197**	.336**							
6. FREQ VIGOROUS EXERCISE	-.120*	-.008	.124*	-.228**	-.172**						
7. PROB OF LIVING TO 75	-.136	.258*	.304**	-.444**	-.213	-.051					
8. PROB OF LIVING TO 85	.000	.024	.079	-.255**	-.025	.103	.724**				
9. TOTAL RECALL	.070	-.174**	.367**	-.149*	-.184**	.047	.185	.155*			
10. SELF-REPORTED MEMORY	-.117*	.063	-.197**	.185**	.274**	.073	-.216	.044	-.164**		
11. COGNITION TOTAL SCORE	.006	-.295**	.500**	-.164*	-.250**	.020	-.175	.037	.898**	-.247**	
12. DEPRESSION	.035	.087	-.228**	.361**	.393**	-.174**	-.214	-.217**	-.204**	-.051	-.243**

$p < .05$. ** $p < .01$. *** $p < .001$

Table 5. Correlation matrix for study variables post-diagnosis

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. GENDER																
2. RACE	-.03															
3. EDUCATION	-.03	-.28**														
4. AGE AT DIAGNOSIS	.07	.04	-.10*													
5. FINANCES ONSET	-.03	-.11*	.26**	.04												
6. CHEMOTHERAPY	-.04	-.01	-.02	-.27**	.02											
7. SURGERY	.04	-.08	-.04	-.06	-.08	.03										
8. RADIATION	-.03	-.02	.06	-.16**	.08	.18**	-.14*									
9. SELF-REP HEALTH	.04	.10*	-.17**	-.05	-.05	.10	-.09	-.02								
10. DIFFICULTY ADL'S	-.01	.06	-.10*	.14**	-.02	-.08	-.09	-.03	.23**							
11. VIG EXERCISE	-.06	-.01	.11*	-.09	.05	-.02	.01	-.01	-.19**	-.14**						
12. PROB LIVING TO 75	-.04	.39**	.03	-.10	.09	.13	.08	.08	-.37*	-.24	.32*					
13. PROB LIVING TO 85	-.06	.04	.01	-.11	.09	-.02	-.04	-.03	-.32**	-.04	.12	.81**				
14. TOTAL RECALL	.14**	-.17**	.34**	-.31**	.13*	.13*	.07	.06	-.10	-.25**	.08	.04	.01			
15. SELF-R MEMORY	-.12**	.08	-.12*	.15**	.01	-.05	-.01	.02	.10*	.21**	-.05	-.33*	-.05	-.16**		
16. COGNITION TOT	.05	-.31**	.48**	-.22**	.17**	.12*	.08	.08	-.18**	-.28**	.09	.21	.01	.89**	-.19**	
17. DEPRESSION	.08	.03	-.18**	.03	-.11*	-.06	-.01	-.09	-.36**	.27**	-.17**	-.40**	-.19**	-.21**	-.04	-.29**

* $p < .05$. ** $p < .01$. *** $p < .001$

Table 6. Fit indices for one-four class unconditional growth curve analysis of total recall

Model				
Fit index	One class	Two classes	*Three classes*	Four classes
AIC	6454.49	6191.79	*6091.23*	6086.28
BIC	6481.81	6234.72	*6149.77*	6160.43
SSBIC	6459.60	6199.82	*6102.18*	6100.15
Entropy	-	0.68	*0.74*	0.79
LMR	-	$p<.01$	$p<.001$	$p>.05$
BLRT	-	$p<.001$	$p <.001$	$p>.05$

Note: AIC = Akaike information criterion, BIC = Bayesian information criterion, SSBIC = sample-size-adjusted Bayesian information criterion, LMR = Lo-Mendell-Rubin test, BLRT = bootstrap likelihood-ratio test. Italics indicate the best-fitting number of classes.

Table 7. Multinomial regression estimates for covariate of treatment type

	Covariate	Est.	S.E.
Compared to ***High Recall***			
Middle Recall	Chemotherapy	-1.18	0.40**
	Surgery	0.24	0.46
	Radiation	-0.57	0.47
Low Recall	Chemotherapy	-1.31	0.38**
	Surgery	-0.18	0.47
	Radiation	-0.98	0.52
Compared to ***Low Recall***			
High Recall	Chemotherapy	1.31	0.38**
	Surgery	0.18	0.47
	Radiation	0.98	0.52
Middle Recall	Chemotherapy	0.13	0.39
	Surgery	0.42	0.38
	Radiation	0.41	0.51

*$p<.05$, **$p<.01$

Table 8. Logistic regression predicting treatment with radiation

Predictor variable	*B*	*SE B*	*β*
Constant	2.42	1.76	11.27
Finances at Onset	.147	.119	1.16
Years of Education	.027	.050	1.03
Race	-.014	.457	.986
Age at Onset	-.06	1.76	.939**

* $p < .05$. ** $p < .01$. *** $p < .001$. -2 Log likelihood = 285.42; Nagelkerke $R^2 = .06$

Table 9. Logistic regression predicting treatment with surgery

Predictor variable	*B*	*SE B*	*β*
Constant	-.102	1.50	.903
Finances at Onset	-.649	.390	.523
Years of Education	.036	.040	1.04
Race	-.726	.448	.484
Age at Onset	-.013	.016	.903

* $p < .05$. ** $p < .01$. *** $p < .001$. -2 Log likelihood = 379.68; Nagelkerke $R^2 = .04$

Table 10. Logistic regression predicting treatment with chemotherapy

Predictor variable	*B*	*SE B*	*β*
Constant	5.82	1.36	337.1
Finances at Onset	.109	.112	1.12
Years of Education	-.045	.035	.956
Race	-.097	.332	.908
Age at Onset	-.082	.016	.921***

* $p < .05$. ** $p < .01$. *** $p < .001$. -2 Log likelihood = 440.7; Nagelkerke $R^2 = .11$

Table 11. Multinomial regression estimates for depression as a covariate

	Covariate	Est.	S.E.
Compared to ***Middle Recall***			
Low Recall	Depression Pre	0.13	0.10
	Depression Post	0.17	0.10*
High Recall	Depression Pre	0.02	0.17
	Depression Post	-0.27	0.13
Compared to ***Low Recall***			
High Recall	Depression Pre	-0.11	0.17
	Depression Post	-0.44	0.13**
Middle Recall	Depression Pre	-0.13	0.10
	Depression Post	-0.17	0.10*

*$p<.05$, **$p<.01$

Table 12. Multinomial regression estimates for health variables as covariates

	Covariate	Est.	S.E.
Compared to ***High Recall***			
Middle Recall	Self-Reported Health Pre	0.06	0.19
	Prob. Living 85 Pre	-0.02	0.01*
	Difficulty with ADLs Post	0.57	0.46
Low Recall	Self-Reported Health Pre	0.17	0.24
	Prob. Living 85 Pre	-0.02	0.01**
	Difficulty with ADLs Post	1.08	0.46*
Compared to ***Middle Recall***			
High Recall	Self-Reported Health Pre	-0.06	0.19
	Prob. Living 85 Pre	0.02	0.01*
	Difficulty with ADLs Post	-0.57	0.46
Low Recall	Self-Reported Health Pre	0.11	0.23
	Prob. Living 85 Pre	-0.01	0.01
	Difficulty with ADLs Post	0.51	0.22*

*$p<.05$, **$p<.01$

Table 13. Multinomial regression estimates for demographic variables as covariates

	Covariate	Est.	S.E.
Compared to ***High Recall***			
Middle Recall	Age	0.13	0.03***
	Gender	-1.22	0.40**
	Education Level	-0.27	0.07***
	Finances	-0.14	0.14
	Marital Status	-0.78	0.42
Low Recall	Age	0.26	0.04***
	Gender	-1.96	0.50***
	Education Level	-0.54	0.09***
	Finances	-0.21	0.19
	Marital Status	-1.09	0.51*
Compared to ***Low Recall***			
High Recall	Age	-0.26	0.04***
	Gender	1.96	0.50***
	Education Level	0.54	0.09***
	Finances	0.21	0.19
	Marital Status	1.09	0.51*
Middle Recall	Age	-0.13	0.03***
	Gender	0.74	0.39
	Education Level	0.27	0.08***
	Finances	0.07	0.19
	Marital Status	0.31	0.41

*p<.05, **p<.01, ***p<.001

Figure 1. Three class unconditional model of total recall trajectories

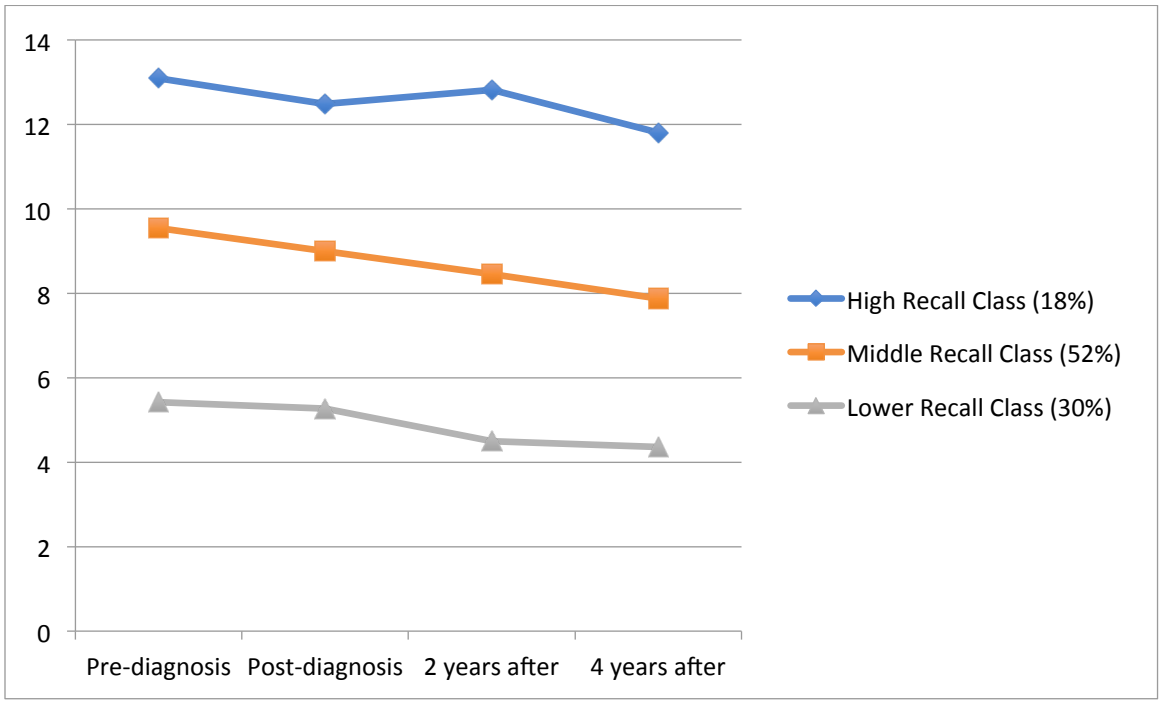
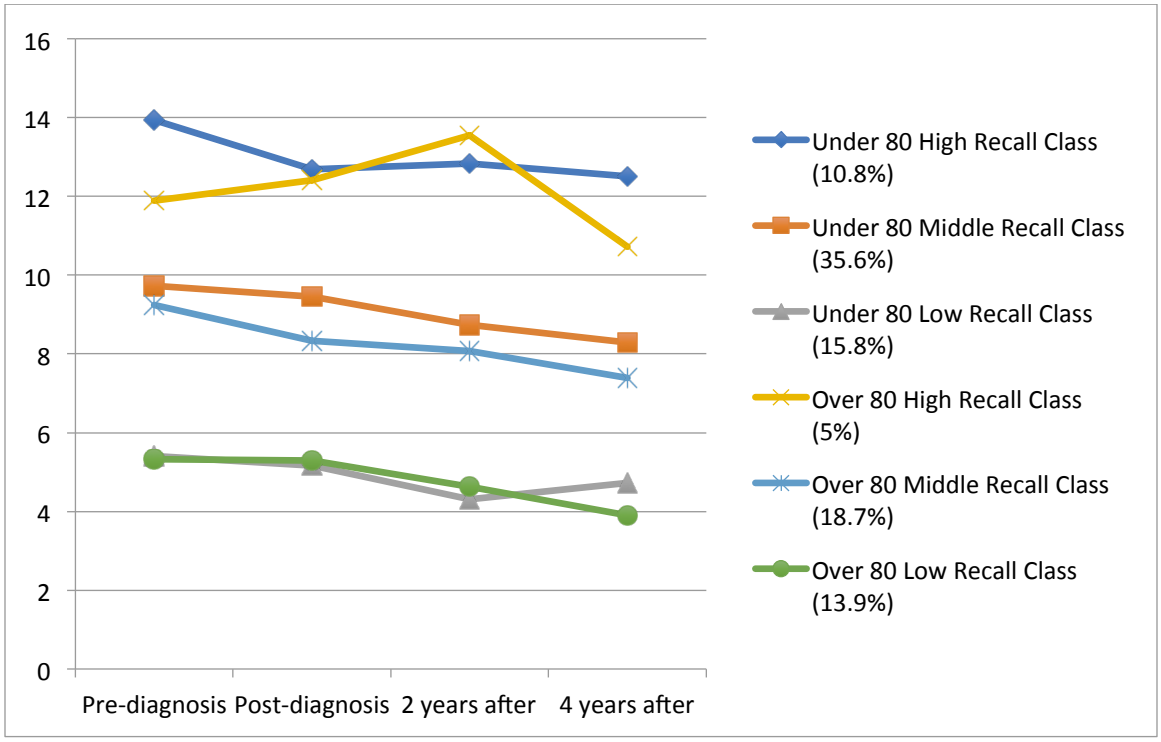


Figure 2. Three class conditional model of total recall with known class (by age)



References

Ahles, T. A., Saykin, A. J., Furstenberg, C. T., Cole, B., Mott, L. A., Skalla, K., ... & Silberfarb, P. M. (2002). Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *Journal of Clinical Oncology*, *20*(2), 485-493.

Ahles, T. A., & Saykin, A. J. (2007). Candidate mechanisms for chemotherapy-induced cognitive changes. *Nature Reviews Cancer*, *7*(3), 192-201.

Altman, D. G., & Lyman, G. H. (1998). Methodological challenges in the evaluation of prognostic factors in breast cancer. *Breast cancer research and treatment*, *52*(1-3), 289 303.

Anderson, N. D., Iidaka, T., Cabeza, R., Kapur, S., McIntosh, A. R., & Craik, F. I. (2000). The effects of divided attention on encoding-and retrieval-related brain activity: A PET study of younger and older adults. *Journal of Cognitive Neuroscience*, *12*(5), 775-792.

Anderson-Hanley, C. A. Y., Sherman, M. L., Riggs, R., Agocha, V., & Compas, B. E. (2003). Neuropsychological effects of treatments for adults with cancer: a meta-analysis and review of the literature. *Journal of the International Neuropsychological Society*, *9*(07), 967-982.

Anstey, K. J., von Sanden, C., Salim, A., & O'Kearney, R. (2007). Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *American Journal of Epidemiology*, *166*(4), 367-378.

Ardila, A., Ostrosky-Solis, F., Rosselli, M., & Gómez, C. (2000). Age-related cognitive decline during normal aging: the complex effect of education. *Archives of Clinical Neuropsychology*, *15*(6), 495-513.

Argyriou, A. A., Assimakopoulos, K., Iconomou, G., Giannakopoulou, F., & Kalofonos, H. P. (2011). Either called "chemobrain" or "chemofog," the long-term chemotherapy induced cognitive decline in cancer survivors is real. *Journal of Pain and Symptom Management, 41*(1), 126-139.

Atkinson, H. H., Rosano, C., Simonsick, E. M., Williamson, J. D., Davis, C., Ambrosius, W. T., ... & Rubin, S. M. (2007). Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(8), 844-850.

Au, R., Seshadri, S., Wolf, P. A., Elias, M. F., Elias, P. K., Sullivan, L., ... & D'Agostino, R. B. (2004). New norms for a new generation: cognitive performance in the Framingham offspring cohort. *Experimental Aging Research*, *30*(4), 333-358.

Bäckman, L., Jones, S., Berger, A. K., Laukka, E. J., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology*, *19*(4), 520.

Baskar, R., Lee, K. A., Yeo, R., & Yeoh, K. W. (2012). Cancer and radiation therapy: current advances and future directions. *International Journal of Medical Science*, *9*(3), 193-199.

Blazer, D. G. (2003). Depression in late life: review and commentary. *Journals of Gerontology Series A*, *58*(3), 249-265.

Bond, M., Bowling, A., McKee, D., Kennelly, M., Banning, A. P., Dudley, N., ... & Martin, A. (2003). Does ageism affect the management of ischaemic heart disease?. *Journal of Health Services Research & Policy*, *8*(1), 40-47.

Brenner, H., Gondos, A., & Arndt, V. (2007). Recent major progress in long-term cancer patient survival disclosed by modeled period analysis. *Journal of Clinical Oncology*, *25*(22), 3274-3280.

Brezden, C. B., Phillips, K., Abdolell, M., Bunston, T., &Tannock, I. F. (2000). Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *Journal of Clinical Oncology, 18*, 2695–2701.

Burgess, C., Cornelius, V., Love, S., Graham, J., Richards, M., & Ramirez, A. (2005). Depression and anxiety in women with early breast cancer: five year observational cohort study. *British Medical Journal*, *330*(7493), 702.

Burton, C. L., Galatzer-Levy, I. R., & Bonanno, G. A. (2014). Treatment type and demographic characteristics as predictors for cancer adjustment: Prospective trajectories of depressive symptoms in a population sample. *Health Psychology*, *34*(6), 602.

Butters, N., Grant, I., Haxyb, J., Judd, L. L., Martin, A., McClelland, J. ... & Stover, E. (1990). Assessment of AIDS-related cognitive changes: Recommendations of the NIMH Workshop on Neuropsychological Assessment Approaches. *Journal of Clinical and Experimental Neuropsychology*, *12*(6), 963-978.

Butters, M. A., Becker, J. T., Nebes, R. D., Zmuda, M. D., Mulsant, B. H., Pollock, B. G., & Reynolds III, C. F. (2000). Changes in cognitive functioning following treatment of late life depression. *American Journal of Psychiatry*.

Campbell, D. T., Stanley, J. C., & Gage, N. L. (1963). *Experimental and Quasi-experimental Designs for Research* (No. 04; Q175, C3.). Boston: Houghton Mifflin.

Castellon, S. A., Ganz, P. A., Bower, J. E., Peterson, L., Abraham, L., & Greendale, G. A. (2004). Neurocognitive performance in breast cancer survivors exposed to adjuvant

chemotherapy and tamoxifen. *Journal of Clinical and Experimental Neuropsychology, 26*, 955–969.

Chochinov, H. M. (2001). Depression in cancer patients. *The Lancet Oncology*,*2*(8), 499-505.

Cimprich, B., Reuter-Lorenz, P., Nelson, J., Clark, P. M., Therrien, B., Normolle, D., ... & Welsh, R. C. (2010). Prechemotherapy alterations in brain function in women with breast cancer. *Journal of Clinical and Experimental Neuropsychology*, *32*(3), 324-331.

Cole, M. G., & Dendukuri, N. (2003). Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *American Journal of Psychiatry, 160*, 1147-1156.

Comijs, H. C., Deeg, D. J. H., Dik, M. G., Twisk, J. W. R., & Jonker, C. (2002). Memory complaints; the association with psycho-affective and health problems and the role of personality characteristics: a 6-year follow-up study. *Journal of Affective Disorders*, *72*(2), 157-165.

Corbett, J. B., & Mori, M. (1999). Medicine, media, and celebrities: News coverage of breast cancer, 1960–1995. *Journalism & Mass Communication Quarterly*, *76*(2), 229-249.

Cortes, J., & Saura, C. (2010). Nanoparticle albumin-bound (nab™)-paclitaxel: improving efficacy and tolerability by targeted drug delivery in metastatic breast cancer. *European Journal of Cancer Supplements*, *8*(1), 1-10.

Craik, F. I. M.. (1994). Memory Changes in Normal Aging. *Current Directions in Psychological Science*, *3*(5), 155–158.

Darzi, A., & Mackay, S. (2002). Recent advances in minimal access surgery. *British Medical Journal*, *324*(7328), 31.

Deimling, G. T., Kahana, B., Bowman, K. F., & Schaefer, M. L. (2002). Cancer survivorship and psychological distress in later life. *Psycho□Oncology*, *11*(6), 479-494.

Derogatis, L. R., Morrow, G. R., Fetting, J., Penman, D., Piasetsky, S., Schmale, A. M., ... & Carnicke, C. L. (1983). The prevalence of psychiatric disorders among cancer patients. *Journal of the American Medical Association*, *249*(6), 751-757.

Donovan, K. A., Small, B. J., Andrykowski, M. A., Schmitt, F. A., Munster, P., & Jacobsen, P. B. (2005). Cognitive functioning after adjuvant chemotherapy and/or radiotherapy for early stage breast carcinoma. *Cancer*, *104*(11), 2499-2507.

Dorval, M., Maunsell, E., Deschenes, L., Brisson, J., & Masse, B. (1998). Long-term quality of life after breast cancer: comparison of 8-year survivors with population controls. *Journal of Clinical Oncology, 16*, 487–494.

Edwards, B. K., Howe, H. L., Ries, L. A., Thun, M. J., Rosenberg, H. M., Yancik, R., ... & Feigal, E. G. (2002). Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on US cancer burden. *Cancer*, *94*(10), 2766 2792.

ELBeltagy, M., Mustafa, S., Umka, J., Lyons, L., Salman, A., Tu, C. Y. G., ... & Wigmore, P. M. (2010). Fluoxetine improves the memory deficits caused by the chemotherapy agent 5 fluorouracil. *Behavioural Brain Research*, *208*(1), 112-117.

Falleti, M. G., Sanfilippo, A., Maruff, P., Weih, L., & Phillips, K. A. (2005). The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. *Brain and Cognition*, *59*(1), 60-70.

Ferguson, R. J., & Ahles, T. A. (2003). Low neuropsychologic performance among adult cancer survivors treated with chemotherapy. *Current Neurology and Neuroscience reports*, *3*(3), 215-222.

Fratiglioni, L., Paillard-Borg, S., & Winblad, B. (2004). An active and socially integrated lifestyle in late life might protect against dementia. *The Lancet Neurology*, *3*(6), 343-353.

Freedman, V. A., Spillman, B. C., Andreski, P. M., Cornman, J. C., Crimmins, E. M., Kramarow, E., ... & Seeman, T. E. (2013). Trends in late-life activity limitations in the United States: an update from five national surveys. *Demography*, *50*(2), 661-671.

Freeman, J. R., & Broshek, D. K. (2002). Assessing cognitive dysfunction in breast cancer: what are the tools?. *Clinical Breast Cancer*, *3*, S91-S99.

Galatzer-Levy, I. R., & Bonanno, G. A. (2014). Optimism and death predicting the course and consequences of depression trajectories in response to heart attack. *Psychological Science*, doi: 0956797614551750.

Gotay, C. C., & Muraoka, M. Y. (1998). Quality of life in long-term survivors of adult-onset cancers. *Journal of the National Cancer Institute, 90*(9), 656-667.

Green, D., Nail, L. M., & Fieler, V. K. (1994). A comparison of patient-reported side effects among three chemotherapy regimens for breast cancer. *Cancer Practice, 2*, 57–62.

Han, L., Gill, T. M., Jones, B. L., & Allore, H. G. (2015). Cognitive aging trajectories and burdens of disability, hospitalization and nursing home admission among community living older persons. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*.

Harrington, C. B., Hansen, J. A., Moskowitz, M., Todd, B. L., & Feuerstein, M. (2010). It's not over when it's over: long-term symptoms in cancer survivors—a systematic review. *The International Journal of Psychiatry in Medicine*, *40*(2), 163-181.

Hebert, L. E., Scherr, P. A., Bienias, J. L., Bennett, D. A., & Evans, D. A. (2003). Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Archives of Neurology*, *60*(8), 1119-1122.

Heflin, L. H., Meyerowitz, B. E., Hall, P., Lichtenstein, P., Johansson, B., Pedersen, N. L., & Gatz, M. (2005). Cancer as a risk factor for long-term cognitive deficits and dementia. *Journal of the National Cancer Institute*, *97*(11), 854-856.

Heflin, M. T., Pollak, K. I., Kuchibhatla, M. N., Branch, L. G., & Oddone, E. Z. (2006). The impact of health status on physicians' intentions to offer cancer screening to older women. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *61*(8), 844-850.

Hewitt, M., Rowland, J. H., & Yancik, R. (2003). Cancer survivors in the United States: age, health, and disability. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *58*(1), 82-91.

Hilverda, K., Bosma, I., Heimans, J. J., Postma, T. J., Vandertop, W. P., Slotman, B. J., ... & Klein, M. (2010). Cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment: initial findings. *Journal of Neuro-oncology*, *97*(1), 89-94.

Hipkins, J., Whitworth, M., Tarrier, N., & Jayson, G. (2004). Social support, anxiety and depression after chemotherapy for ovarian cancer: a prospective study. *British Journal of Health Psychology*, *9*(4), 569-581.

Howlader, N., Noone, A. M., Krapcho, M., Neyman, N., Aminou, R., Waldron, W., & Edwards,

B. K. (Eds.). (2011). *SEER Cancer Statistics Review, 1975–2008*. Bethesda, MD: National Cancer Institute. Retrieved from http://seer.cancer.gov/csr/1975_2008/

Hurria, A., Balducci, L., Naeim, A., Gross, C., Mohile, S., Klepin, H., ... & Figlin, R. (2008). Mentoring junior faculty in geriatric oncology: report from the Cancer and Aging Research Group. *Journal of Clinical Oncology*, *26*(19), 3125-3127.

Hurria, A., Naylor, M., & Cohen, H. J. (2013). Improving the quality of cancer care in an aging population: recommendations from an IOM report. *Journal of the American Medical Association*, *310*(17), 1795-1796.

Idler, E. L., & Benyamini, Y. (1997). Self-rated health and mortality: a review of twenty-seven community studies. *Journal of Health and Social Behavior*, 21-37.

Janssen-Heijnen, M. L., Maas, H. A., Houterman, S., Lemmens, V. E., Rutten, H. J., & Coebergh, J. W. W. (2007). Comorbidity in older surgical cancer patients: Influence on patient care and outcome. *European Journal of Cancer*,*43*(15), 2179-2193.

Jenkins, V., Shilling, V., Deutsch, G., Bloomfield, D., Morris, R., Allan, S., ... & Winstanley, J. (2006). A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *British Journal of Cancer*, *94*(6), 828-834.

Jung, T., & Wickrama, K. A. S. (2008). An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychology Compass*, *2*(1), 302-317.

Juster, F. T., & Suzman, R. (1995). An overview of the Health and Retirement Study. *Journal of Human Resources*, S7-S56.

Kahana, E., Bhatta, T., Lovegreen, L. D., Kahana, B., & Midlarsky, E. (2013). Altruism, helping, and volunteering pathways to well-being in late life. *Journal of Aging and Health*, *25*(1), 159-187.

Karlamangla, A. S., Miller-Martinez, D., Aneshensel, C. S., Seeman, T. E., Wight, R. G., & Chodosh, J. (2009). Trajectories of cognitive function in late life in the United States: demographic and socioeconomic predictors .*American Journal of Epidemiology*.

Keating, N. L., Nørredam, M., Landrum, M. B., Huskamp, H. A., & Meara, E. (2005). Physical and Mental Health Status of Older Long Term Cancer Survivors. *Journal of the American Geriatrics Society*, *53*(12), 2145-2152.

Keefe, R. S. (2016). Treating cognitive impairment in depression: an unmet need. *The Lancet Psychiatry, 3*(5), 392-393.

King, S. (2004). Pink Ribbons Inc: breast cancer activism and the politics of philanthropy. *International Journal of Qualitative Studies in Education*, *17*(4), 473-492.

Kinsella, K. G., & Wan, H. E. (2009). *An Aging World: 2008*. US Department of Commerce, Economics and Statistics Administration, US Census Bureau.

Kohout, F. J., Berkman, L. F., Evans, D. A., & Cornoni-Huntley, J. (1993). Two shorter forms of the CES-D depression symptoms index. *Journal of Aging and Health*, *5*(2), 179-193.

Kreukels, B. P., Schagen, S. B., Ridderinkhof, K. R., Boogerd, W., Hamburger, H. L., & van Dam, F. S. (2005). Electrophysiological correlates of information processing in breast cancer patients treated with adjuvant chemotherapy. *Breast Cancer Research and Treatment*, *94*(1), 53-61.

Kreukels, B. P., Schagen, S. B., Ridderinkhof, K. R., Boogerd, W., Hamburger, H. L., Muller, M. J., & van Dam, F. S. (2006). Effects of high-dose and conventional-dose adjuvant chemotherapy on long-term cognitive sequelae in patients with breast cancer: an electrophysiologic study. *Clinical Breast Cancer*,*7*(1), 67-78.

Krtolica, A., & Campisi, J. (2002). Cancer and aging: a model for the cancer promoting effects of the aging stroma. *The International Journal of Biochemistry & Cell Biology*, *34*(11), 1401-1414.

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., & Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine*, *144*(2), 73-81.

Leung, S., LoGiudice, D., Schwarz, J., & Brand, C. (2011). Hospital doctors' attitudes towards older people. *Internal Medicine Journal*, *41*(4), 308-314.

Levy, B., Ashman, O., & Dror, I. (2000). To be or not to be: The effects of aging stereotypes on the will to live. *Omega-Journal of Death and Dying*, *40*(3), 409-420.

Levy, B. R. (2003). Mind matters: Cognitive and physical effects of aging self-stereotypes. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *58*(4), P203-P211.

Li, S. C., Lindenberger, U., & Sikström, S. (2001). Aging cognition: from neuromodulation to representation. *Trends in Cognitive Sciences*, *5*(11), 479-486.

Lubke, G. H., & Muthén, B. (2005). Investigating population heterogeneity with factor mixture models. *Psychological Methods*, *10*(1), 21.

Massman, P. J., Delis, D. C., Butters, N., Levin, B. E., & Salmon, D. P. (1990). Are all subcortical dementias alike?: Verbal learning and memory in Parkinson's and Huntington's disease patients. *Journal of Clinical and Experimental Neuropsychology*, *12*(5), 729-744.

Massman, P. J., Delis, D. C., Butters, N., Dupont, R. M., & Gillin, J. C. (1992). The subcortical dysfunction hypothesis of memory deficits in depression: neuropsychological validation

in a subgroup of patients. *Journal of Clinical and Experimental Neuropsychology*, *14*(5), 687-706.

McCaffrey, R. J., Duff, K., & Westervelt, H. J. (Eds.). (2000). *Practitioner's Guide to Evaluating Change with Neuropsychological Assessment Instruments*. Springer Science & Business Media.

McClintock, S. M., Husain, M. M., Greer, T. L., & Cullum, C. M. (2010). Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. *Neuropsychology*, *24*(1), 9.

McGuire, L. C., Ford, E. S., & Ajani, U. A. (2006). Cognitive functioning as a predictor of functional disability in later life. *The American Journal of Geriatric Psychiatry*, *14*(1), 36-42.

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*(1), 33-44.

McEwen, B. S. (2002). Sex, stress and the hippocampus: Allostasis, allostatic load and the aging process. *Neurobiology of Aging, 23*, 921-939.

Mesholam-Gately, R. I., Giuliano, A. J., Zillmer, E. A., Barakat, L. P., Kumar, A., Gur, R. C., ... & Moberg, P. J. (2012). Verbal learning and memory in older adults with minor and major depression. *Archives of Clinical Neuropsychology*,*27*(2), 196-207.

Midlarsky, E., & Hannah, M. E. (1989). The generous elderly: naturalistic studies of donations across the life span. *Psychology and Aging*, *4*(3), 346.

Midlarsky, E., & Kahana, E. (2007). Life course perspectives on altruism, health, and mental health. In S. G. Post (Ed.), *Altruism and health outcomes: Perspectives from empirical research* (pp. 56-69). New York: Oxford University Press.

Midlarsky, E., Kahana, E., & Belser, A. (2015). Prosocial Behavior in Late Life. In D. Schroeder & W. Graziano (Eds.) *Oxford Handbook of Prosocial Behavior*, pp. 415-432. New York: Oxford University Press, pg. 415.

Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., & Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet*, *370*(9590), 851-858.

Muthen, B. O., & Muthen, L. K. (1998-2010). *Mplus User's Guide* (Sixth Edition ed.). Los Angeles, CA: Muthen & Muthen.

Peake, M. D., Thompson, S., Lowe, D., & Pearson, M. G. (2003). Ageism in the management of lung cancer. *Age and Ageing*, *32*(2), 171-177.

Phillips, K. A., & Bernhard, J. (2003). Adjuvant breast cancer treatment and cognitive function: current knowledge and research directions. *Journal of the National Cancer Institute*, *95*(3), 190-197.

Pienta, A. M., Hayward, M. D., & Jenkins, K. R. (2000). Health consequences of marriage for the retirement years. *Journal of Family Issues*, *21*(5), 559-586.

Piras, F., Cherubini, A., Caltagirone, C., & Spalletta, G. (2011). Education mediates microstructural changes in bilateral hippocampus. *Human Brain Mapping*, *32*(2), 282 289.

Polsky, D., Doshi, J. A., Marcus, S., Oslin, D., Rothbard, A., Thomas, N., & Thompson, C. L. (2005). Long-term risk for depressive symptoms after a medical diagnosis. *Archives of Internal Medicine*, *165*(11), 1260-1266.

Porter, K. E. (2013). “Chemo Brain”—Is Cancer Survivorship Related to Later-Life Cognition? Findings From the Health and Retirement Study. *Journal of Aging and Health*, *25*(6), 960 981.

Proust-Lima, C., Amieva, H., Letenneur, L., Orgogozo, J. M., Jacqmin-Gadda, H., & Dartigues, J. F. (2008). Gender and education impact on brain aging: a general cognitive factor approach. *Psychology and Aging*, *23*(3), 608.

Puts, M. T. E., Papoutsis, A., Springall, E., & Tourangeau, A. E. (2012). A systematic review of unmet needs of newly diagnosed older cancer patients undergoing active cancer treatment. *Supportive Care in Cancer*, *20*(7), 1377-1394.

Rabbitt, P., Donlan, C., Watson, P., McInnes, L., & Bent, N. (1995). Unique and interactive effects of depression, age, socioeconomic advantage, and gender on cognitive performance of normal healthy older people. *Psychology and Aging*, *10*(3), 307.

Radloff, L. S. (1977). The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385-401.

RAND HRS Data, Version M. Produced by the RAND Center for the Study of Aging, with funding from the National Institute on Aging and the Social Security Administration. Santa Monica, CA (September 2014).

Reitan R. M., Wolfson D. (1993). *The Halstead-Reitan neuropsychological test battery: theory and clinical interpretation.* Tucson: Neuropsychology Press.

Roe, C. M., Xiong, C., Miller, J. P., & Morris, J. C. (2007). Education and Alzheimer disease without dementia support for the cognitive reserve hypothesis. *Neurology*, *68*(3), 223 228.

Rolig, R. L., & McKinnon, P. J. (2000). Linking DNA damage and neurodegeneration. *Trends in Neurosciences*, *23*(9), 417-424.

Rosenthal, R. (1965). The volunteer subject. *Human Relations*, *18*(4), 389.

Salinsky, M. C., Storzbach, D., Dodrill, C. B., & Binder, L. M. (2001). Test–retest bias, reliability, and regression equations for neuropsychological measures repeated over a 12 16-week period. *Journal of the International Neuropsychological Society*, *7*(5), 597-605.

Salthouse, T. (2009). *Major issues in cognitive aging*. Oxford University Press.

Sarkisian, C. A., Hays, R. D., & Mangione, C. M. (2002). Do older adults expect to age successfully? The association between expectations regarding aging and beliefs regarding healthcare seeking among older adults. *Journal of the American Geriatrics Society*, *50*(11), 1837-1843.

Schagen, S. B., Muller, M. J., Boogerd, W., Rosenbrand, R. M., Van Rhijn, D., Rodenhuis, S., & van Dam, F. S. A. M. (2002). Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. *Annals of Oncology*, *13*(9), 1387 1397.

Schoevers, R. A., Beekman, A. T. F., Deeg, D. J. H., Geerlings, M. I., Jonker, C., & Van Tilburg, W. (2000). Risk factors for depression in later life; results of a prospective community based study (AMSTEL). *Journal of Affective Disorders*, *59*(2), 127-137.

Schroyen, S., Adam, S., Jerusalem, G., & Missotten, P. (2015). Ageism and its clinical impact in oncogeriatry: state of knowledge and therapeutic leads. *Clinical Interventions in Aging*, *10*, 117.

Seeman, T. E., McEwen, B. S., Rowe, J. W., & Singer, B. H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of the National Academy of Sciences*, *98*(8), 4770-4775.

Seeman, T. E., Crimmins, E., Huang, M. H., Singer, B., Bucur, A., Gruenewald, T., ... & Reuben, D. B. (2004). Cumulative biological risk and socio-economic differences in mortality: MacArthur studies of successful aging. *Social Science & Medicine*, *58*(10), 1985-1997.

Shaffer, V. A., Merkle, E. C., Fagerlin, A., Griggs, J. J., Langa, K. M., & Iwashyna, T. J. (2012). Chemotherapy was not associated with cognitive decline in older adults with breast and colorectal cancer: findings from a prospective cohort study. *Medical Care*, *50*(10), 849.

Shrira, A., Palgi, Y., Ben-Ezra, M., Spalter, T., Kavé, G., & Shmotkin, D. (2011). For better and for worse: The relationship between future expectations and functioning in the second half of life. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, gbq103.

Siegel, R., DeSantis, C., Virgo, K., Stein, K., Mariotto, A., Smith, T., ... & Lin, C. (2012). Cancer treatment and survivorship statistics, 2012. *CA: A Cancer Journal for Clinicians*, *62*(4), 220-241.

Silberfarb, P. M., Philibert, D., & Levine, P. M. (1980). Psychosocial aspects of neoplastic disease: II. Affective and cognitive effects of chemotherapy in cancer patients. *The American Journal of Psychiatry*.

Silberfarb, P. M. (1983). Chemotherapy and cognitive defects in cancer patients. *Annual review of medicine*, *34*(1), 35-46.

Slamon, D. J., Romond, E. H., & Perez, E. A. (2006). Advances in adjuvant therapy for breast cancer. *Clinical Advances in Hematology & Oncology: H&O*, *4*(3).

Smith, B. D., Smith, G. L., Hurria, A., Hortobagyi, G. N., & Buchholz, T. A. (2009). Future of cancer incidence in the United States: burdens upon an aging, changing nation. *Journal of Clinical Oncology*, *27*(17), 2758-2765.

Sonnega, A., Faul, J. D., Ofstedal, M. B., Langa, K. M., Phillips, J. W., & Weir, D. R. (2014). Cohort profile: the Health and Retirement Study (HRS). *International Journal of Epidemiology*, *43*(2), 576-585.

Steffick, D. E. (2000). Documentation of affective functioning measures in the Health and Retirement Study. Ann Arbor, MI: HRS Health Working Group.

Stemmer, S. M., Stears, J. C., Burton, B. S., Jones, R. B., & Simon, J. H. (1994). White matter changes in patients with breast cancer treated with high-dose chemotherapy and autologous bone marrow support. *American Journal of Neuroradiology*, *15*(7), 1267 1273.

Stern, Y. (2003). The concept of cognitive reserve: a catalyst for research. *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 589-593.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015-2028.

Tabbarah, M., Crimmins, E. M., & Seeman, T. E. (2002). The relationship between cognitive and physical performance MacArthur Studies of Successful Aging. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *57*(4), M228-M235.

Taylor, M. J., & Heaton, R. K. (2001). Sensitivity and specificity of WAIS–III/WMS–III demographically corrected factor scores in neuropsychological assessment. *Journal of the International Neuropsychological Society*, *7*(07), 867-874.

Tchen, N., Juffs, H. G., Downie, F. P., Yi, Q. L., Hu, H., Chemerynsky, I., ... & Tannock, I. F. (2003). Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology*, *21*(22), 4175 4183.

Townsley, C. A., Selby, R., & Siu, L. L. (2005). Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *Journal of Clinical Oncology*, *23*(13), 3112-3124.

Vardy, J., Wong, K., Yi, Q. L., Park, A., Maruff, P., Wagner, L., & Tannock, I. F. (2006). Assessing cognitive function in cancer patients. *Supportive Care in Cancer*, *14*(11), 1111-1118.

Vardy, J., & Tannock, I. (2007). Cognitive function after chemotherapy in adults with solid tumours. *Critical Reviews in Oncology/Hematology*, *63*(3), 183-202.

Vearncombe, K. J., & Pachana, N. A. (2009). Impact of health, treatment and psychological factors on cognitive functioning after chemotherapy for early breast cancer. *Australian Psychologist*, *44*(4), 235-247.

Wefel, J. S., Cloughesy, T., Zazzali, J. L., Zheng, M., Prados, M., Wen, P. Y., ... & Friedman, H. S. (2011). Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab. *Neuro-oncology*, *13*(6), 660-668.

Wefel, J. S., & Schagen, S. B. (2012). Chemotherapy-related cognitive dysfunction. *Current Neurology & Neuroscience Report, 12*, 267-275.

Whalley, L. J., Deary, I. J., Appleton, C. L., & Starr, J. M. (2004). Cognitive reserve and the neurobiology of cognitive aging. *Ageing Research Reviews*, *3*(4), 369-382.

Whittington, C. J., Podd, J., & Kan, M. M. (2000). Recognition memory impairment in Parkinson's disease: power and meta-analyses. *Neuropsychology*, *14*(2), 233.

Wolinsky, F. D., Bentler, S. E., Hockenberry, J., Jones, M. P., Obrizan, M., Weigel, P. A., ... & Wallace, R. B. (2011). Long-term declines in ADLs, IADLs, and mobility among older Medicare beneficiaries. *BMC Geriatrics*, *11*(1), 43.

Wurm, S., Tesch-Römer, C., & Tomasik, M. J. (2007). Longitudinal findings on aging-related cognitions, control beliefs, and health in later life. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *62*(3), P156-P164.

Yancik, R. (1997). Cancer burden in the aged. *Cancer*, *80*(7), 1273-1283.

Yancik, R., Ganz, P. A., Varricchio, C. G., & Conley, B. (2001). Perspectives on comorbidity and cancer in older patients: approaches to expand the knowledge base. *Journal of Clinical Oncology*, *19*(4), 1147-1151.

Yellen, S. B., Cella, D. F., & Leslie, W. T. (1994). Age and clinical decision making in oncology patients. *Journal of the National Cancer Institute*, *86*(23), 1766-1770.

Zunini, R. A. L., Scherling, C., Wallis, N., Collins, B., MacKenzie, J., Bielajew, C., & Smith, A. M. (2013). Differences in verbal memory retrieval in breast cancer chemotherapy patients compared to healthy controls: a prospective fMRI study. *Brain Imaging and Behavior*, *7*(4), 460-477.